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# PROGNOSIS IN POSTENCEPHALITIC DISORDERS

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The present study of prognosis in encephalitic sequelae has been motivated by an interest in the subsequent course of 51 carefully studied cases of encephalitis which were reported by Kennedy.[1] Aside from any intrinsic value in terms of prognosis which this study may have, the hope of obtaining some additional tools for therapy has been kept in mind. A personal sense of helplessness in attempting to offer recommendations to parents who are burdened with a serious postencephalitic disorder of behavior on the part of a member of the family probably has been the strongest motivating factor. The practice usually has been for the family to endure the patient in the home as long as possible and then to send him to a state institution. Few states have adequate facilities for the management of such disorders, aside from simple custodial care, which is of great benefit to the patient's family but is of little rehabilitative value to the patient. I have designated as "uncontrolled" those patients who have been cared for in the home or custodial institution as opposed to those placed in the "controlled" environment of a special school with the privilege of having active psychiatric therapy.

Although my interest in postencephalitic sequelae is not limited to disorders of behavior, as is shown by the accompanying follow-up study of 51 cases representing all types of residua, in my opinion the field of behavior disorders holds the greatest promise of benefits from therapy or at least deserves the most investigation. Sequelae of an objective neurologic character, such as parkinsonism, have been extensively investigated, in spite of the fact that little rehabilitation has been effected. It has become apparent that, at best, this process may only be arrested. Other symptoms, such as disturbances of sleep and of respiration and tics, tend to improve without treatment. But the behavior disorder unassociated with evidence of physical or neurologic damage, although

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1. Kennedy, R. L. J.: Prognosis of Sequelae of Epidemic Encephalitis in Children, Am. J. Dis. Child. **28**:158 (Aug.) 1924.

potentially the sequela most amenable to therapy, is probably the most neglected. The children with such disorders appear normal, except for aspects of their volitional behavior which are often as bewildering to themselves as to their parents. In addition to statistical information with which to guide recommendations for the management of these patients, it is earnestly hoped that a worth while critical analysis of the "uncontrolled" method versus the "controlled" or supervised method may be offered. The legitimate assumption is that the latter method markedly excels the former, but so far as is known large series of cases with a sufficient lapse of time for comparison of early and late results have not been reported.

The excellent reports of Bond and his associates [2] on the organization of a school for the treatment of these postencephalitic problems of behavior unaccompanied by objective neurologic disease are standard references in the field of therapeutics. Gibbs,[3] also, has contributed to this field with the report of the King's Park State Hospital project, by which a special department for children who have encephalitic sequelae was created. These reports supply a nucleus of authentic data for comparison with average outpatients, in the treatment of whom a relatively unsystematized regimen has been followed.

It is apparent that a great number of questions are presented which need solution, such as: What is the optimal period for reeducation of these children? Do they recover to the point of adult social adjustment without special training or are they misfits all their lives? Is there any period after which they may be assured that they are free from the threat of more serious neurologic sequelae? Except for a painful period of disturbed behavior, will the patients "outgrow" their disorders if left alone? It is hoped that a review of a comparatively large series of cases will give valuable clues if not the complete answers to such questions as these.

## MATERIAL FOR PRESENT STUDY

The material for study has been limited to children who were 14 years of age or less at the time of their first admission to the Mayo Clinic. Such a limitation offers many advantages. First, it may reasonably be assumed that less pathologic change due to other diseases is present in children than in adults, and, therefore, one may follow more

2. (*a*) Bond, E. D., and Appel, K. E.: The Treatment of Behavior Disorders Following Encephalitis, New York, Commonwealth Fund, 1931. (*b*) Bond, E. D., and Partridge, G. E.: Post-Encephalitic Behavior Disorders in Boys and Their Management in a Hospital, Am. J. Psychiat. **6**:25 (July) 1926. (*c*) Bond, E. D., and Smith, L. H.: Post-Encephalitic Behavior Disorders: A Ten Year Review of Franklin School, ibid. **92**:17 (July) 1935.

3. Gibbs, C. E.: Behavior Disorders in Chronic Epidemic Encephalitis: Clinical Course in Relation to Signs of Persisting Organic Pathology, Am. J. Psychiat. **9**:619 (Jan.) 1930.

accurately the course of encephalitis in them. Second, behavior disorders as postencephalitic sequelae occur almost exclusively in childhood and adolescence. Still another advantage is that a study of children offers greater opportunity for obtaining accurate follow-up studies through the parents as observers than is offered by depending on the patients themselves for accurate self judgment.

Since 1918 there have been more than 1,000 cases of acute encephalitis and postencephalitic disorders diagnosed in children at the Mayo Clinic. The majority of such patients had passed through the acute episode of the disease elsewhere, and it was necessary to depend on a history of headaches, fever, visual disturbances, disorders of sleep and, occasionally, on the results of examination of the spinal fluid for knowledge of the nature of the initial infection. In spite of the protean manifestations of the acute phase of encephalitis, it was found that by adhering to these criteria original diagnoses made elsewhere often proved to be as reliable as those made when the patient was personally observed in the acute phase.

There is a remarkable dearth of pathologic studies of these patients who have no obvious evidence of neurologic disease. Behavior disorders of a pure type do not directly decrease the expectancy of life, and, since recognition of such of these disorders as are due to encephalitis has been evident only during the past fifteen years, it is reasonable to assume that little pathologic material of such a nature has been available. A complete histologic study of even 1 authentic case of encephalitis with an uncomplicated residual disorder of behavior would do much to clarify the present status of knowledge concerning "functional" postencephalitis.

## CAUSATION AND SYMPTOMS

Etiologic studies over the past twenty years have yielded a wealth of speculation regarding the actual causative agent of encephalitis, but little authentic information has been derived. At present, it appears that the most tenable hypothesis is that the agent is a filtrable virus. With regard to behavior disorders, however, there are no specific features that indicate whether the agent responsible is a virus or some other factor, such as trauma. This situation suggests that damage in the disease is structural and not, as has been advanced to explain the pathogenesis, due to a specific neurotoxin.

It is postulated that many postencephalitic states are actually chronic, progressive encephalitis. Occasionally, encephalitis occurs so insidiously that the diagnosis hinges on recognition of the sequelae. Witness the 5 cases reported by Burr,[4] in 1925, in which an acute illness had not been present.

4. Burr, C. W.: Sequelae of Epidemic Encephalitis Without any Preceding Acute Illness (Chronic Encephalitis): Report of Cases, Arch. Neurol. & Psychiat. **14**:20 (July) 1925.

Work on immunization has led to production of vaccines and serums which are believed by certain workers [5] to influence favorably the course of acute encephalitis. Ziegler,[6] in 1928, reporting a death rate of 4.3 per cent with the use of vaccine as compared to 24 per cent without vaccine, gave statistical support to this hypothesis; but, in spite of this, the results in terms of social recovery a few years later demonstrated no appreciable difference between vaccine-treated and untreated patients. It is possible, in view of the striking improvement noted in some patients after the use of serum, that serum therapy may still play an important part in the attenuation of the sequelae in children, in whom damage may be diffuse.

Symptoms have been so widely discussed in their varied manifestations as to make any comment superfluous. In disturbances of behavior it is extremely important to establish the occurrence of some episode, usually febrile, followed by behavior which showed a definite change. There is, however, a character to the impulsive, exaggerated, involuntary, emotional response that gives the trained observer valuable clues and usually suggests the diagnosis.

## PROGNOSIS

It has been suggested in the objectives initially enumerated that the principal weakness of prognostic concepts relating to behavior disorders has been the lack of elapsed time sufficient for observing the results in these children in their adult life. That the social aspect of this problem is important may be well learned from any teacher, social worker or member of a community who has had intimate contact with any of these children. The final social adjustment of these children, if favorable, may make the effort expended to achieve it well worth while. If, on the contrary, they are social obstructionists and dependents, more concerted action must be taken by physicians, teachers and social agencies to provide institutions, or special units in already existing institutions, for a more rational type of treatment than is possible with the unsystematized management customary in the home. The workability of just such units is seen in the Franklin School of the Pennsylvania Hospital and in the units at King's Park Hospital and Rockland State Hospital. I do not believe it necessary to go into the economic aspects of such projects, as it is impossible to list all the benefits in certified balance sheets dealing only with dollars and cents. The damage resulting from destructive habits of these children may be expressed in

5. Rosenow, E. C.: Streptococci in Relation to Etiology of Epidemic Encephalitis, J. Infect. Dis. **34**:329 (April) 1924.

6. Ziegler, L. H.: Follow-Up Studies on Persons Who Have Had Epidemic Encephalitis, J. A. M. A. **91**:138 (July 21) 1928.

dollars and cents, but this figure represents only a small part of the effects produced, the undesirable influence on other children being of infinitely greater importance.

Comprehensive surveys of sequelae of encephalitis have been conducted by numerous workers; the most recent reports give prognostic data decidely different from the tentative estimates of ten or fifteen years ago. For example, in 1921 Grossman [7] suggested that approximately 70 per cent of those afflicted with acute encephalitis make a good functional recovery. He arrived at such a figure by allowing 20 per cent for deaths occurring in the acute stages and 10 per cent for the incidence of progressive disease of the central nervous system. However, he revised these figures [8] a year later, and a much less favorable prognosis was given. He found that 24 patients of 92 who had had acute encephalitis were normal or occupationally sufficient one to three years later, and 4 showed some improvement, whereas the condition of 62 patients was worse than formerly and of 2 had remained stationary. This means an incidence of recovery of about 33 per cent. W. L. Holt Jr.,[9] in 1937, found only 11.5 per cent of 78 patients seen in the acute stage of the disease alive, well and free of sequelae ten to sixteen years after the initial infection. However, Holt's figures are changed to 36 per cent by inclusion of those patients with social recovery and exclusion of the deaths due to the acute phase, criteria used by Grossman.[8] Thus, close agreement exists between two representative studies of patients who survived the acute phase of encephalitis, in spite of the great difference in the length of the periods of observation.

Somewhat different considerations enter into prognostic studies in children. There is general agreement that encephalitis in children less than 5 years of age carries a decided danger of resulting mental deficiency. Other sequelae, such as tics, disturbances of sleep and respiration, metabolic disorders, convulsions and changes in personality, are more frequent in children than in adults.

Statistically, one must be careful to distinguish between the prognosis of acute encephalitis and the prognosis of its sequelae. The acute phase in children carries a mortality between 10 and 15 per cent. Howe [10] gave 11 per cent as the mortality in the acute phase in children. However, I am dealing with those patients who have had sequelae, and

7. Grossman, M.: Late Results in Epidemic Encephalitis, Arch. Neurol. & Psychiat. **5**:580 (May) 1921.

8. Grossman, M.: Sequels of Acute Epidemic Encephalitis, J. A. M. A. **78**: 959 (April 1) 1922.

9. Holt, W. L., Jr.: Epidemic Encephalitis: A Follow-Up Study of Two Hundred and Sixty-Six Cases, Arch. Neurol. & Psychiat. **38**:1135 (Dec.) 1937.

10. Howe, H. A.: Prognosis for Epidemic Encephalitis in Children, Bull. Johns Hopkins Hosp. **47**:123 (Sept.) 1930.

therefore I am concerned with prognosis in terms of social adjustment rather than in terms of the immediate mortality rate. In 1923, Ebaugh [11] studied 17 cases of acute encephalitis associated with sequelae and predicted recovery to the extent of social compatibility of 50 per cent of the patients, on the basis of 5 patients who apparently recovered and 3 whose condition was improving.

In Holt's [9] group of 43 children with behavior disorders only 25.6 per cent had attained social recovery some ten years later. This figure compares favorably with that of 23.5 per cent (20 recovered patients of 85) offered by Bond and Smith,[2c] in 1935 in their report on the treatment of behavior disorders in the Franklin School. It would be fallacious to assume that the close agreement of these reports gives a true estimate of the general run of results in disorders of behavior in patients in "controlled" (special school) and "uncontrolled" (home) environments, for it is granted that any school would draw predominantly severely affected patients, at least seriously enough affected to be brought to the attention of the referring physician or social worker by the harassed parents. Furthermore, it is reasonable to suppose that the criteria for determining recovery are more strict in such intensively studied patients than in those in the uncontrolled environment. Actually, of 85 patients, 80 showed tendencies toward improvement during treatment in the Franklin School, but only 20 satisfactorily maintained that adjustment after returning home.

It is generally accepted that the prognosis in behavior disorders is more favorable than that in other sequelae of encephalitis, and, since disorders of behavior have their highest incidence in children, it might be concluded that encephalitic sequelae in children are of less serious import than they are in adults. This conclusion is found to be seriously questionable, however, after following up these patients over a greater length of time. The example, cited by Howe,[10] of a patient who showed in 1922 typical evidence of change in personality and who died in 1925 with full-blown parkinsonism, is not an exception. In case 34 of the group reported in this paper almost complete recovery was noted ten years after the initial infection, but definite evidence of parkinsonism was found on reexamination in 1938, fourteen years after the original attack of encephalitis.

Nevertheless, there is justification for adopting a relatively more hopeful attitude toward the behavior disorders. The absence of objective neurologic signs and the theoretically greater recoverability of children may be held as definite assets in prognosis until proved otherwise.

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11. Ebaugh, F. G.: Neuropsychiatric Sequelae of Acute Epidemic Encephalitis, Am. J. Dis. Child. **25**:89 (Feb.) 1923.

In Kennedy's report in 1924, of 51 cases of encephalitis, for which this paper serves as a follow-up study, the sequelae had been present for from one to five years. It was possible to obtain additional information concerning 40 of these patients through reexamination at the clinic and communications from them, their relatives or their physicians, offered spontaneously or in response to a questionnaire. This questionnaire dealt with the patient particularly from the standpoint of present health, social state, intellectual level and disorders of behavior, sleep, respiration and motility. The validity of reports given by relatives is always questionable, but in the few instances in which I had the opportunity to obtain a report from the local physician or personally to examine the patient, as in cases 6 and 49 for example, I found that the condition was in close agreement with that indicated by the answers to the questionnaire. In no instance was there an appreciable discrepancy in information from two different sources. It was assumed, therefore, that the questionnaires were reliable indicators of the patients' present status. Apparently the disturbances of habitual behavior and the infirmities were sufficiently striking to warrant honest reporting by the most enthusiastic optimist (as the parent usually was found to be).

Only the 40 cases in which it was possible to obtain some information about the present status were used in comparing the progress reported in 1924 with that reported at the present time. Case 27 was not included in this comparison because of the death of the patient shortly before publication of the first review. These cases are divided into three groups according to the duration of sequelae up to the time of the latest report. In those cases in which death has intervened, whether due to the process of the disease or to some intercurrent cause, the period of sequelae is calculated to the date of death, a procedure which statistically has increased materially the number of patients with sequelae that have been present less than ten years.

In estimating the course of the sequelae I have adopted, on the whole, ratings similar to those used by Howe [10] in his well organized report concerning 66 children who had had encephalitis. Howe, thinking in terms of social usefulness, used the terms "complete incapacity," "partial incapacity" (with clinical signs of organic lesions but without progression) and "recovery." Recovery may include some clinical residuum or some slight subjective symptoms but not both. These ratings roughly conform to the criteria used in connection with my simple terminology of "worse," "unchanged or stationary" and "improved" to denote the condition stated in the report of 1924, which I have designated in tables 1 and 3 by the symbols —, = and +, respectively. Table 1 contains these comparative figures.

TABLE 1.—*Comparative Summary of Cases of Encephalitis*

| Case | Age in Years | Sex | Date of Appearance of Sequelae | First Summary Report, 1923-1924 | Progress* | Date of Last Report | Duration of Sequelae, Yr. | Second Summary Report, 1939 | Treatment | Progress Since First Report* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 14 | M | 1919 | Ataxia; nystagmus; slowed activity; changed disposition; irritable | — | 1939 | 20 | Dependent; walks without crutches; head tremors; irritable; sullen | Period of simple hospitalization | — |
| 2 | 12 | F | 1919 | Parkinsonism; blurred vision; tremor; mentally retarded; refractory behavior | = | 1939 | 20 | Dependent; tremor and weakness of right extremities; good natured; 2 years of high school; defective speech | 1 month in sanatorium; 300 chiropractic treatments | = |
| 3 | 2 | F | 1919 | Unable to walk or talk; requires constant care; has screaming and nervous spells; mentally deficient | = | 1936 | 17 | Physically and mentally definitely retarded; died in 1936 of pneumonia | In school for feebleminded | Died |
| 4 | 1½ | M | 1918 | Mute; blind in right eye; cares for self | = | 1939 | 21 | Good general health; deaf-mute; blind in right eye; emotionally controlled; finished eighth grade; cobbler apprentice | In school for deaf and dumb | *= |
| 5 | 11 | F | 1923 | Sleep inversion; changed personality; excessive praying | = | 1939 | 16 | Self-supporting as medical technician; irritable; fatigue; physically sound | Attended high school away from home | + |
| 6 | 12 | M | 1919 | Changed personality; irascible; frequent headache, nosebleeds; in school for feebleminded and state reformatory | = | 1937 | 18 | Numerous commitments to state institutions for crimes ranging from forgery to sexual assault | In school for feebleminded | — |
| 7 | 12 | M | 1920 | Parkinsonism; walks poorly; irritable; speech impaired | = | 1927 | 7 | Parkinsonism with bulbar symptoms; impulsive activity | | — |
| 8 | 7 | F | 1920 | Changed personality; tantrums; irascibility; spastic right leg; strabismus | = | 1939 | 19 | Parkinsonism; huge appetite; obese; emotional difficulty; vicious; contrary; finished fifth grade only | Period in orthopedic hospital | — |
| 9 | 2 | F | 1918 | Right hemiplegia; unable to talk; insomnia; convulsions | — | .... | .. | Unable to trace | | |
| 10 | 3 | M | 1920 | Unable to walk or talk; purposeless acts | + | 1929 | 9 | Died in 1929 of mastoid complications; had recovered markedly | | Died |
| 11 | 4½ | M | 1919 | Respiratory syndrome; restless sleep; cares for self; petit mal seizures | — | 1927 | 8 | Not improved; no specific details | | = |
| 12 | 13 | F | 1922 | Respiratory syndrome; dyspnea when recumbent; insomnia and night terrors | + | 1935 | 8 | Died by suicide in 1935 of phenobarbital poisoning; three former attempts at suicide; always nervous; gonorrhea, 1930; respiratory disturbance until 1930, when she recovered suddenly | Christian science | Died |
| 13 | 9 | M | 1919 | Parkinsonism; unable to care for self; speech impaired; mentally retarded; irritable | — | .... | .. | Unable to trace | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 10 | F | 1920 | Slow movements; hypersomnolence; speech slow, but patient able to care for self; some respiratory difficulty; mentally retarded | + | 1928 | 8 | Somewhat slower activity; difficulty in swallowing until death of influenza and pneumonia in 1928 | | Died |
| 15 | 8 | M | 1921 | Parkinsonism; able to feed self; changed personality; no progress in school | = | .... | .. | Unable to trace | | |
| 16 | 11 | M | 1920 | Sleep disturbance improving; fatigability; cares for self; changed personality | + | 1933 | 13 | Practically helpless, in bed 20 hours daily; difficulty in chewing; indistinct speech | Numerous medications; slight response to atropine | — |
| 17 | 9 | M | 1920 | Parkinsonism; requires help; irritable; restless | = | 1932 | 12 | Died in 1932 of pneumonia; grew progressively worse until death, becoming a complete invalid | | Died |
| 18 | 10 | M | 1920 | Parkinsonism with left-sided weakness and salivation; personality change; irritability; huge appetite | — | 1932 | 12 | Died in 1932; "steadily worse until death" | | Died |
| 19 | 2½ | M | 1922 | Convulsions | + | 1939 | 17 | General condition good; congenital cataracts; convulsions controlled with phenobarbital; intelligence normal | | + |
| 20 | 9 | M | 1919 | Parkinsonism; almost helpless; respiratory syndrome with noisy breathing | — | .... | .. | Unable to trace | | |
| 21 | 1⅛ | F | 1919 | Respiratory difficulty improving but helpless; mentally deficient | — | 1930 | 20 | Poor physical state; slow; weak; little use of extremities; sleep and respiration disturbed; irritable and unmanageable; mentally deficient | | — |
| 22 | 8 | M | 1920 | Changed personality; very emotional; antisocial; hallucinations; in school for feebleminded; drowsiness prominent | + | 1939 | 19 | General health good; activity slowed; irritable at times; has torticollis; I. Q., 93; in institution | In school for feebleminded | — |
| 23 | 12 | F | 1920 | Respiratory syndrome; convulsions which cleared; nervous; dependent; partly cares for self; mentally retarded | — | .... | .. | Unable to trace | | |
| 24 | 6 | M | 1920 | Sleep disturbance; occasional respiratory disturbance; quarrelsome; talkative; polydipsia; urinary incontinence | + | 1929 | 10 | Physical state good except for marked tremor; impulsive behavior; temper tantrums; abusive; respiration and water metabolism corrected | In state epileptic colony | = |
| 25 | 5 | F | 1918 | Personality changes; preoccupied; mental retardation but obeys commands well; in school for defectives | = | 1939 | 21 | General health good but weakness and stiffness of legs; mentally deficient; does not talk; occasionally irritable; has tantrums | At Vineland, N. J., school until age of 10 | = |

TABLE 1.—*Comparative Summary of Cases of Encephalitis—Continued*

| Case | Age in Years | Sex | Date of Appearance of Sequelae | First Summary Report, 1923-1924 | Progress* | Date of Last Report | Duration of Sequelae, Yr. | Second Summary Report, 1939 | Treatment | Progress Since First Report* |
|---|---|---|---|---|---|---|---|---|---|---|
| 26 | 7 | M | 1919 | Occasional hyperpnea; changed personality; restless; infantile | + | 1939 | 20 | Physical state poor; many tremors; unable to feed self; difficulty in swallowing; oculogyric crises; quick temper; highly emotional; intelligence fair | | − |
| 27 | 11 | M | 1919 | Parkinsonism; behavior change; died in 1923 of intercurrent infection | Died | .... | .. | Not included in statistics of second report | | |
| 28 | 10 | M | 1919 | Parkinsonism; wilful; mischievous; intelligence normal | + | .... | .. | Unable to trace | | |
| 29 | 11 | M | 1920 | Parkinsonism; unable to walk, talk distinctly or care for self | = | 1925 | 5 | Became gradually more helpless; bulbar symptoms developed; died in 1925 | | Died |
| 30 | 9 | M | 1922 | Respiratory syndrome; cares for self | + | 1939 | 17 | Partially self-supporting as assistant postal carrier; nervous, irritable but controllable; finished high school; drags one foot; voice changed and less distinct | Christian science | = |
| 31 | 6 | M | 1922 | Respiration and sleep disturbance; speech impaired; irritable; average intelligence | + | 1939 | 17 | Partially self-supporting as furrier; finished high school; breathes heavily and head twists at times but is improving | | + |
| 32 | 6 | F | 1920 | Parkinsonism; sleep disturbance | + | 1934 | 14 | Gradually weaker with parkinsonism; died in 1934 | | Died |
| 33 | 8 | F | 1921 | Parkinsonism; no effort to walk; changed personality; irritable and nervous; refuses to study | = | 1939 | 18 | Very poor condition; unable to move limbs; emaciated; convulsions spontaneously disappeared | | − |
| 34 | 8 | F | 1923 | Compulsive, rapid speech but moves slowly; superior intelligence | + | 1938 | 15 | Right-sided weakness and tremor; parkinsonism with salivation since 1937; nervous; impulsive behavior; eloped; married twice | | − |
| 35 | 8 | M | 1922 | Parkinsonism; unable to care for self | = | .... | .. | Dependent, walks only with help; parkinsonism; oculogyric crises; emotionally controlled; intelligence fair | Solution of posterior pituitary; electricity | = |
| 36 | 9 | F | 1923 | Behavior change; quick temper; night terrors; intelligence good | + | 1929 | 6 | Brief note from patient appealing for work; apparently largely recovered by 1929 | | + |
| 37 | 9½ | F | 1923 | Sleep disturbance; restless at night; respiratory disturbance | = | 1939 | 16 | Physical state good; emotional control fair but antagonistic to mother; mentally retarded; not incompetent | | = |
| 38 | 11 | F | 1921 | Parkinsonism; unable to care for self | = | .... | .. | Unable to trace | | |
| 39 | 7 | F | 1923 | Changed personality; irritable, restless, tense, unmanageable behavior; salivation; marked expectoration; speech not clear | + | 1928 | 5 | Progressive left-sided paralysis; some involvement of right side; dependent; feels urge to misbehave; has severe headaches | | = |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 40 | 11 | M | 1921 | Respiratory syndrome; changed personality; irritable; unmanageable; intelligence average | = | 1927 | 6 | Necessary to institutionalize because of refractory behavior, on recommendation of school authorities | | = |
| 41 | 4 | M | 1923 | Changed personality; nervous; walks very little; grand mal seizures with mental deterioration | = | .... | .. | Unable to trace | | |
| 42 | 2 | M | 1922 | Changed personality; irritable; fits of temper; rapid respiration; frequent swallowing | + | 1930 | 17 | Physically appears normal; petit mal seizures controlled with phenobarbital; slightly lowered emotional control; short breath; senior in high school; mother oversolicitous | In special school | + |
| 43 | 13 | F | 1917 | Sleep disturbance and respiratory syndrome | = | 1930 | 7 | Died in 1930; "cause unknown" | | Died |
| 44 | 8 | F | 1921 | Parkinsonism; eyes turned upward; disobedient behavior; polyphagia; bilateral palsy, seventh nerve | = | 1927. | 6 | No improvement; "terrible suffering and care" | | = |
| 45 | 7 | M | 1919 | Sleep disturbance until 1921; parkinsonism; salivation; polydypsia; changed personality; very restless | = | .... | .. | Unable to trace | | |
| 46 | 9 | F | 1919 | Sleep disturbance improving; parkinsonism progressing | = | 1930 | 11 | "Still living but completely paralyzed" | | — |
| 47 | 12 | M | 1923 | Sleep disturbance improving; respiratory syndrome; intelligence good | + | 1939 | 16 | Partly self-supporting; studying art; health fair; nervous at times; finished junior college | | + |
| 48 | 11 | M | 1920 | Respiratory syndrome accompanied by postural change; in school for feebleminded | = | .... | .. | Unable to trace | | |
| 49 | 12 | M | 1923 | Sleep and respiratory disturbances; both improving | + | 1939 | 16 | Dependent; very thin and weak; stiff walk; apparent parkinsonism; oculogyric episodes; finished tenth grade | Tried everything; now on benzedrine sulfate | — |
| 50 | 7 | F | 1922 | Respiratory syndrome with postural changes; breath-holding to state of falling | = | 1928 | 6 | "Gradually better" until state of good health | | + |
| 51 | 7 | M | 1919 | Sleep disturbance; parkinsonism with hemiparesis and slow speech; obesity; gained 25 pounds (9 Kg.) in 2 years | = | 1929 | 10 | Advanced parkinsonism; unable to talk; progressive since last visit | | — |

* In this column — signifies that the condition is worse; =, that it is unchanged or stationary, and +, that it is improved.

The highest death rate is in the first few years after the onset of sequelae, after which, apparently, there is a tendency for the more hopelessly afflicted patients to adjust to a vegetative form of existence. As has been stated before, the normal expectancy of life for the age attained does not alter the mortality at that age.

The postencephalitic process definitely contributed to 6 of the 9 reported deaths. This conclusion is based on such statements as "steadily worse until death" and "gradually became unable to move." In 1 of the other 3 cases in which death occurred the "cause was unknown." The second of these 3 cases had been reported by Parker,[12] in 1930, as a postencephalitic respiratory syndrome; this patient committed suicide five years after her alleged recovery from the encephalitis. This recovery is a moot question as her general emotional reaction, tension and restlessness may well have been accentuated by the encephalitis. In the third of these 3 cases death was due to intercurrent infection, but this patient

TABLE 2.—*Status of Forty Children with Encephalitic Sequelae*

| | Results According to Report of 1924 | | | Results According to Subsequent (Present) Report | | | |
|---|---|---|---|---|---|---|---|
| Duration of Sequelae, in Years | Improved | Stationary | Worse | Improved | Stationary | Worse | Died |
| 15 or more | 10 | 10 | 2 | 5 | 8 | 8 | 1 |
| 10 to 14 | 2 | 8 | 1 | 0 | 0 | 3 | 3 |
| 5 to 9 | 5 | 6 | 1 | 2 | 4 | 1 | 5 |
| Total | 17 | 19 | 4 | 7 | 12 | 12 | 9 |
| Per cent | 42.5 | 47.5 | 10 | 17.5 | 30 | 30 | 22.5 |

previously had been reported as "markedly recovered." It is possible that the deaths in the aforementioned 3 cases may have been unrelated to the encephalitis, although it is doubtful that these 3 patients were completely free of symptoms. Theoretically, I might add these 3 cases to the group of 7 in which recovery occurred (table 2), making a total of 10 cases in which improvement was shown. The percentage of recovery then would be changed from 17.5 to 25.0 per cent.

This rate of recovery agrees closely with that given in other reports, but it is well to remember that this is giving the fullest benefit of all doubt to the better prognosis. It appears that the most hopeful figure representing the incidence of recovery in these children is considerably less than 30 per cent. If the 21 patients who are still living and whose condition has been followed for "fifteen years or more" are considered, the figures show that 5 of 21 are improved, or an incidence of improvement of 24 per cent. The records of those same 21 patients showed that

12. Parker, H. L.: Epidemic Encephalitis: Respiratory Syndrome, M. Clin. North America **13**:1347 (May) 1930.

in 1924 the condition of 10 was improved or improving, an incidence of almost 50 per cent. This decrease in percentage of improvement must logically be attributed to the factor of additional lapse of time, which allowed the latent pathologic changes to become manifest.

It is of interest to speculate on the present status of the 10 patients who could not be traced. Six of these 10 patients (cases 13, 15, 20, 28, 38 and 45) had parkinsonism, and 1 (case 9) had right hemiplegia. It is unlikely that improvement took place in any of these 7 patients. Two of the 10 patients (cases 23 and 48) exhibited respiratory disturbances, from which they probably recovered, although the mental retardation noted in each would not be expected to show a change. The remaining patient (case 41) had grand mal seizures, and again the outlook should be considered doubtful. Therefore, at least 8 of these 10 patients carried an unfavorable prognosis. It may be said that the figures derived from study of the 40 cases which were traced are maximally optimistic.

There were few "pure" behavior disorders in the 1924 report. That is to say, although there were 23 patients who definitely showed evidence of change in personality or behavior, many of these had associated objective neurologic symptoms and signs. Actually, only 12 of the 23 patients may be considered as representing a group of behavior disorders according to the acceptable criterion advanced by Bond and Appel,[2a] namely, that of excluding any patients in whom objective neurologic signs were found.

These 12 patients with behavior disorders had, in addition, other sequelae of encephalitis, principally disturbances of respiration and sleep; but these sequelae may also be considered as disorders of function without demonstrable structural damage. Kennedy [1] noted that the disturbances of respiration and sleep tended to decrease; in his series about 50 per cent of the disorders of sleep had disappeared and all of the disorders of respiration were either decreased or unchanged; none had become worse than they previously had been. Therefore, although there were only 3 patients with disordered behavior in Kennedy's original group who did not have some associated syndrome referable also to the encephalitic process (cases 6, 22 and 36), a total of 12 are grouped for special consideration. Table 2 sums up the comparative features of the earlier and present reports.

Since the present status of the 3 patients with "pure" behavior disorders without other associated syndromes is known, it is interesting to note their course subsequent to the first report on them. The patient in case 6, for instance, a boy aged 12 years, was sent to a school for the feebleminded because of having committed arson; this act occurred four years after the initial infection. His intelligence quotient was found to be 88 at that time, and he was transferred to the state reformatory.

At the age of 16 years he was sent to the state hospital for the insane on charges of forgery and assault with intent to rape. He escaped after a short period only to appear a few months later at a reformatory in a neighboring state on a charge of robbery. Then followed a series of escapes and short terms in similar institutions of two states and a sentence in a state penitentiary for sexual perversion involving a 12

TABLE 3.—*Comparative Summary of Course of Patients with Behavior Disorders*

| Case | Report of 1924 | Progress* | Present Report | Progress* |
|---|---|---|---|---|
| 5 | Restless; impulsive; compulsive behavior; intelligence good; sleep disturbed | = | Self-supporting; nervous, but average social adjustment | + |
| 6 | Irritable; antisocial; in reform school | = | History of continual misdemeanors and crimes | — |
| 14 | Irritable; disturbed sleep and respirations; slow perception; has private tutor | + | Died of intercurrent infection in 1928; evidence of parkinsonism | |
| 22 | Very unstable emotionally; in school for feebleminded | + | In institution, but I. Q. is 93; slow activity; torticollis; irritable | = |
| 24 | Quarrelsome; restless; tic-like habits; disturbed sleep and respiration; removed from school | + | In state epileptic hospital; impulsive behavior and often abusive; except for tremor, physically sound | = |
| 25 | Irritable; preoccupied; unstable; mentally deficient; disturbed sleep | = | Weakness; stiffness in legs; cannot talk; irritable; has tantrums; mentally deficient; imbecile | = |
| 26 | Irritable; restless; infantile; mawkish; disturbed sleep | + | Parkinsonism; emotionally volatile | — |
| 31 | Bad temper; marked change of disposition; disturbed sleep | + | Partially self-supporting; some inability plus disturbed respiration occasionally; fairly well controlled | + |
| 36 | Volatile; quick temper; morbid fears | + | Apparently largely recovered as she has reached adult life | + |
| 39 | Irritable; tends to be cruel, aggressive and quarrelsome; sleep disturbed | + | Little or no improvement; still has urge to misbehave; some weakness of right side | = |
| 40 | Irritable; unmanageable; respiratory difficulty | = | Institutionalized on recommendation of school authorities; misdemeanor not known | = |
| 42 | Restless; nervous; eating problem; disturbed respiration | + | Petit mal; controlled with phenobarbital; oversolicitous mother may be problem now | + |

* In this column — signifies that the condition is worse; =, that it is unchanged or stationary, and +, that it is improved.

year old boy. At present, an application is pending for his return to the school for the feebleminded, inappropriate as such a disposition may seem to be.

Another of these patients with "pure" behavior disorders (case 22) is a fairly respectable inmate of a state school for feebleminded in spite of an intelligence quotient of 93. However, he suffers from torticollis in addition to episodes of irritability and unmanageable behavior, which make some form of institutionalization necessary.

The last report concerning the patient in case 36, the third example of "pure" behavior disorder, was received in 1929, when the patient

wrote a well constructed note attempting to obtain work at the clinic. It is assumed that no gross disorder of behavior was evident. These 3 cases (cases 6, 22 and 36), if they may be considered examples of "pure" behavior disorders, show 1 good result in 3. There is a question of constitutional psychopathy in case 6, but in the absence of any evidence of such derangement before the patient's initial illness it must be assumed that the disorder is a sequel of encephalitis. The question of psychopathic personality is mentioned frequently in the evaluation of disorders of behavior; but unless there are significant premorbid evidences of psychopathy, it must be assumed that the encephalitic process is primarily instrumental in determining the subsequent behavior.

It may be seen by the summary in table 3 that the progress noted in the first report is much more favorable than that found at present. Improvement in 8 of these 12 patients, with the other 4 unchanged but no worse, indicates that improvement took place in two thirds of the behavior disorders. The present report on these 12 patients indicates that the condition of 4 is improved, of 5 unchanged or stationary in adjustment and of 2 worse—1 has definite parkinsonism, and the other is a recidivistic criminal. Lastly, 1 is dead from intercurrent infection, although definite evidence of parkinsonism was present before death and must therefore be credited to the encephalitic process.

Of all the sequelae parkinsonism is the most dreaded, certainly from the standpoint of ultimate recovery. Holt [9] cited only 1 case of 100 in which recovery had occurred from parkinsonian signs of tremor and rigidity, which were present in the acute phase. In the present reported series there has not been a single instance of improvement in patients with evidence of parkinsonism as a sequela, and gradual progression of the symptoms contributed to 6 of the 9 reported deaths.

The respiratory syndrome may be considered as relatively benign. Examination of those patients who presented this syndrome in 1924 shows that, aside from 2 deaths associated with other progressive symptoms and 4 patients who could not be traced, there is only 1 patient (case 21) who still has the respiratory disorder, and even in this instance it is not one of the major symptoms.

Disturbances of sleep likewise disappeared with time. In those instances in which such disturbances were present as initial effects all patients who reported have returned to essentially normal habits of sleep.

## SUMMARY AND CONCLUSIONS

Only 17.5 per cent of 40 children with postencephalitic sequelae were improved an average of 13.8 years after onset. A study of this same group in 1924 revealed that 42.5 per cent were improved or improving at that time. The statistical difference is attributed to the elapsed time, which allowed latent pathologic effects to become manifest.

Only 4 of 12 patients with relatively uncomplicated behavior disorders were improved as compared to 8 of the same group who were improving fifteen years previously.

Specific or psychiatrically supervised treatment was not given in any of the cases so far as is known.

Conclusions should not be drawn from the study of this small group except for the suggestion that the prognosis, in general, suffers with the passage of time.

More intensive work on prognosis in postencephalitic behavior disorders should be conducted in order to evaluate methods of management of the patient outside of institutions and to attenuate the attendant social problem.

# SUSPENSION GRASP BEHAVIOR OF THE HUMAN INFANT

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In 1891 Robinson [1] drew attention to the curious ability of the newborn infant to suspend the weight of his body in midair by the strength of his own grip. Since that time the phylogenetic, ontogenetic and neurogenetic import of the phenomenon has received considerable attention. Three major questions which arise in connection with this behavior pattern are:

1. Why should the newborn baby be capable of a striking performance which for him has no recognized utility?

2. What are the essential or outstanding changes in this activity as the child develops from infancy to maturity?

3. In what way do developmental changes in a behavior of this order reflect maturational changes in the central nervous system?

The answer to the first question is still speculative. The theory suggested by Robinson [1] in his original article on "Darwinism in the Nursery" has never been impressively challenged or refuted. The idea that this type of behavior represents a residuum of some primordial function is the one most commonly accepted today. Richter [2] offered supporting evidence when he pointed out the similarity of the reflex in the newborn Macacus rhesus monkey to that in the human baby, the essential differences being the time of suspension and the chronologic age at which the reflex shows definite diminution. Until additional evidence has accumulated or more logical hypotheses have been advanced, it is reasonable to accept the theory that the suspension grasp reflex in the newborn infant represents a residuum of a phyletic function.

Several studies on the reflex [3] have been published which describe some of the changes that occur with growth. On the following features there appear to be general agreement:

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From the Normal Child Development Study of the Department of Pediatrics, Columbia University College of Physicians and Surgeons, and the Babies' Hospital.

1. Robinson, L.: Darwinism in the Nursery, Nineteenth Cent. **30**:831, 1891.

2. Richter, C. P.: The Grasping Reflex in the New-Born Monkey, Arch. Neurol. & Psychiat. **26**:784-790 (Oct.) 1931.

3. (*a*) Richter, C. P.: The Grasp Reflex of the New-Born Infant, Am. J. Dis. Child. **48**:327-332 (Aug.) 1934. (*b*) Halverson, H. M.: Studies of the Grasping Responses of Early Infancy: I., J. Genetic Psychol. **51**:371-449, 1937.

*(Footnote continued on next page)*

1. The reflex can be elicited in practically all newborn infants, though there are exceptions.[8g]

2. The reflex tends to "disappear" or become weaker after the first few months of life.

3. There are individual differences in the strength of the grasp and also in the age at which diminution or "disappearance" of the reflex takes place.

4. Although the reflex is generally present at birth, it attains its maximum strength a few weeks later.

5. There is no appreciable difference in the gripping strengths of the right and left hands of the same child.

6. Subsequent to the reflex phase, "voluntary" or deliberate grasping is manifested.

On the other hand, the literature reveals some confusion or difference of opinion with regard to certain aspects of the phenomenon. Often the disparities in results can be attributed to differences in experimental procedures, as Halverson [8b] has pointed out.

One type of confusion arises out of the tendency to apply the term "grasping reflex" indiscriminately, both to the suspension phenomenon and to the reflex closure of the digits around an object. Evidence will be presented later which suggests that these two reflexes are different in their ontogenetic development and are probably of different phylogenetic origin.

The present report is concerned with the developmental changes of the suspension phenomenon as manifested during the first few years of life. Although the closure of the digits is a factor in the suspension activity, the term "suspension grasp behavior" has been used to distinguish the suspension phenomenon from the grasp reflex.

## EXPERIMENTAL CONDITIONS

The methods employed in studying this behavior were simple. In one situation the fingers of both hands of the baby were placed securely around a small wooden rod; they were held there by the experimenter, and the rod was raised until the baby's body was above the supporting surface. The rod used in suspending the

(*c*) Watson, J. B.: Psychology from the Standpoint of the Behaviorist, Philadelphia, J. B. Lippincott Company, 1919. (*d*) Peiper, A., and Isbert, H.: Ueber die Körperstellung des Säuglings, Jahrb. f. Kinderh. **115**:114-115 and 142-176, 1927. (*e*) Sherman, M.; Sherman, I., and Flory, C. D.: Infant Behavior, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1936, vol. 12, no. 4, pp. 1-107. (*f*) Lyon, R. A.: Reflexes of the Newborn, Schweiz. med. Wchnschr. **67**:689-694, 1937. (*g*) Bryan, E. S.: Variations in the Responses of Infants During the First Ten Days of Postnatal Life, Child Development **1**:56-77, 1930. Robinson.[1]

newborn infants measured 0.8 cm. in diameter and the one for the older babies 1.27 cm. Once the body of the baby was in a suspended position, the experimenter's hands were removed and the baby was allowed to hang by his own grip. By means of a stopwatch a record was kept of the suspension time for both hands. The record covered that interval of time between the removal of the experimenter's hands and the release of the rod by either hand or both hands of the infant. This method favored the longest suspension time of which the baby was capable, since he was placed in a disturbing position before being called on to exercise his own gripping power. Since there was no appreciable difference in the performances of right and left hands in the two hand suspension, the measurements were combined for analysis.

In the second situation a rod was placed in only one hand of the infant while he was lying in a supine position. After he had flexed his fingers around the rod the experimenter raised it upward in order to lift his body from the recumbent to the suspended position. While some effort was made, such as increasing pressure on the palm, to induce the baby to grasp the rod, he was not forced to do so as in the first situation. If the baby held on to the rod with one hand sufficiently to allow his body to be raised above the underlying surface, by means of a stopwatch a record of the suspension time was calculated from the moment his foot left the surface until, releasing his grip, he fell. This situation probably evoked the minimum suspension time. Psychologically, it is quite different from the conditions imposed during two hand suspension. In this experiment the grasp must be so strong that the baby allows himself to be carried from a secure or supported position to an insecure state of suspension. Sometimes the baby grasped the rod sufficiently to allow part of his body—head, shoulders or buttocks—to be raised but released his grip before suspension occurred. Such occurrences portray the difference between the grasp and the suspension grasp behavior. The occasions when only part of the body was elevated do not figure in the measurements obtained with a stopwatch.

## ANALYSIS OF DATA

Measurements of suspension time were obtained at repeated intervals on a group of 91 children over a period of several years. The interval between observations varied; the total number of measurements was 3,121 for two hand suspension, 2,017 for right single hand suspension and 1,827 for the left single hand suspension. The number of measurements obtained at each age level is indicated in tables 1 and 2.

The data were averaged over ten or twenty day intervals during the first three hundred days and over two hundred day intervals thereafter. When the average suspension time is plotted against chronologic age, it can be seen that, starting from a relatively low level immediately after birth, both single hand and double hand suspension reach a maximum at about the end of the first month, and a significant change occurs at the age of about 120 days (curves in *A*, fig. 1). Subsequently, single hand suspension is practically extinct and two hand suspension fluctuates around a low level.

After a period during which the ability to suspend the body is diminished or suppressed, it is reestablished or, in the case of two hand suspension, reenforced. This recurrence of the ability is shown by

the curves in *B* of figure 1. Two hand suspension increases steadily after its reenforcement toward the end of the first year. Single hand suspension appears sporadically during the second year but is not definitely reestablished until the child is about 2½ years old. Qualitative differences in performance of the older children indicate that the later

TABLE 1.—*Number of Observations in Each Twenty Day Interval During the First Three Hundred Days of Life*

| Age in Days | Right Hand | Left Hand | Both Hands |
|---|---|---|---|
| 1- 20 | 90 | 86 | 184 |
| 21- 40 | 58 | 57 | 118 |
| 41- 60 | 62 | 57 | 118 |
| 61- 80 | 58 | 55 | 82 |
| 81-100 | 69 | 63 | 104 |
| 101-120 | 64 | 60 | 86 |
| 121-140 | 65 | 63 | 92 |
| 141-160 | 61 | 58 | 98 |
| 161-180 | 57 | 53 | 84 |
| 181-200 | 61 | 55 | 88 |
| 201-220 | 44 | 44 | 72 |
| 221-240 | 56 | 57 | 84 |
| 241-260 | 50 | 53 | 74 |
| 261-280 | 51 | 54 | 76 |
| 281-300 | 40 | 40 | 60 |

TABLE 2.—*Number of Observations in Each Two Hundred Day Interval*

| Age in Days | Right Hand | Left Hand | Both Hands |
|---|---|---|---|
| 1- 200 | 645 | 607 | 1,054 |
| 201- 400 | 591 | 433 | 622 |
| 401- 600 | 278 | 274 | 438 |
| 601- 800 | 134 | 143 | 286 |
| 801-1,000 | 58 | 56 | 90 |
| 1,001-1,200 | 61 | 63 | 113 |
| 1,201-1,400 | 46 | 46 | 92 |
| 1,401-1,600 | 14 | 14 | 28 |
| 1,601-1,800 | 27 | 27 | 56 |
| 1,801-2,000 | 25 | 25 | 50 |
| 2,001-2,200 | 55 | 56 | 114 |
| 2,201-2,400 | 7 | 7 | 16 |
| 2,401-2,600 | 14 | 14 | 28 |
| 2,601-2,800 | 16 | 16 | 38 |
| 2,801-3,000 | 12 | 13 | 24 |
| 3,001-3,200 | 11 | 11 | 24 |
| 3,201-3,400 | 0 | 0 | 0 |
| 3,401-3,600 | 8 | 7 | 16 |
| 3,601-3,800 | 0 | 0 | 0 |
| 3,801-4,000 | 15 | 15 | 32 |

achievements are deliberate or voluntary. The curve in figure 2 shows the trend of suspension behavior for all ages from birth to 8 years.

For 60 of the 91 children there was a sufficient number of repeated observations to identify the age of "disappearance" or suppression of the single hand reflex suspension grasp. This age for each child was arbitrarily selected as the first twenty day interval during which no suspension was elicited. From the distribution curve in figure 3 it is seen that the modal age for the suppression of the single hand suspension was about 90 days. By 210 days of age all of the children had passed through this phase of suspension activity.

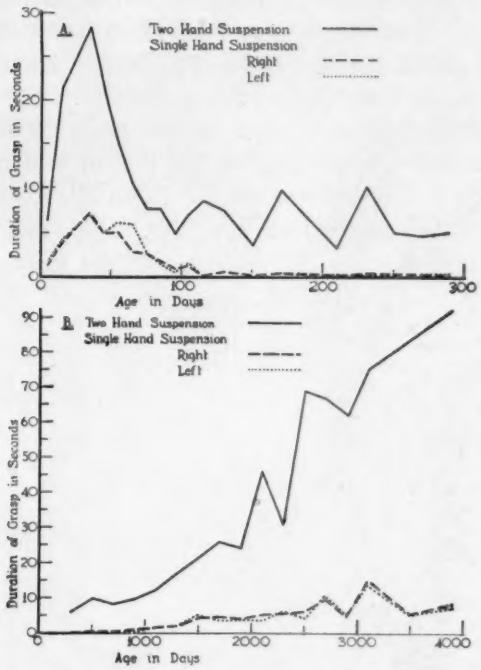


Fig. 1.—Curves showing the suspension time for the group of children: *A*, suspension time averaged over ten day intervals during the first four months and over twenty day intervals thereafter; *B*, that averaged over two hundred day intervals after the age of 300 days.

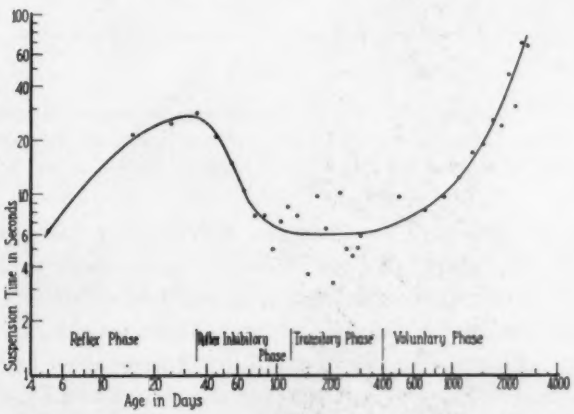


Fig. 2.—Suspension time for the group of children plotted on a logarithmic scale against chronologic age, showing the trend of suspension behavior for all ages up to 8 years.

The developmental trend of the activity is more clearly delineated by longitudinal (daily) measurements on several individual children. Variation in two hand suspension time at different age periods is shown for these children in figures 4 and 5. Included among the curves are measurements on 2 sets of identical twin boys. The striking similarity in both pairs of curves is noted by comparing the curve for Peter Dalton with that of his twin, Charles, and that of Hilton Putney with his brother Hugh's. The lower curve for Allan Nicholson is drawn to the same scale as the other individual curves. When the ordinate interval is expanded (upper curve), the trend of the suspension time for

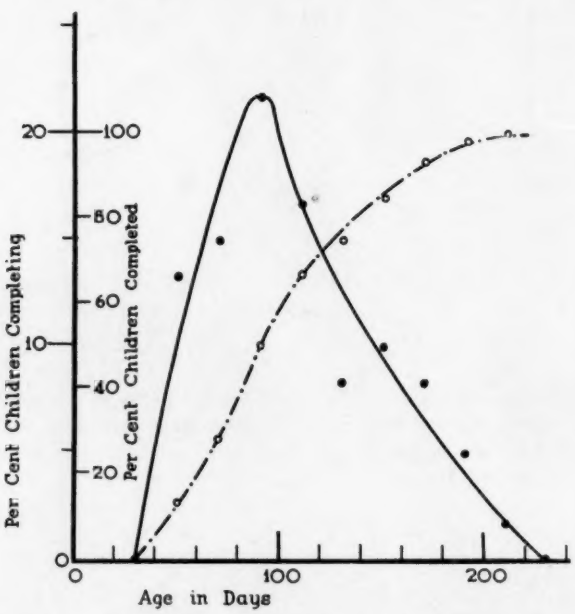


Fig. 3.—The solid line shows the modal age for the evanescence of the reflex phase of single hand suspension. The ogive curve indicates the total percentage of children who had completed the reflex single hand suspension at any age.

Allan is more apparent. These curves indicate that the general trend is essentially the same, despite individual differences in suspension time, that is, children in whom the suspension behavior is weak show characteristic changes of the same order as those in whom it is strong.

Curves showing the course of single hand suspension as manifested by individual children are still more revealing (figs. 6 and 7). All of these curves show that the suspension time is relatively low at birth, increases during the first month, begins to decline about the beginning of the second month and is practically extinct by the end of the fourth month. There are individual differences both in suspension time and in the

age at which extinction is clearly evident. There are also individual differences in the age at which voluntary suspension becomes established. Two of the children, Patricia Shelley and Jane Woods, were too young when this report was prepared to have begun the voluntary phase of their development. In all of these individual curves, however, the extinction period for single hand suspension is more clearly defined and extends over a longer age span than is indicated for the similar period of diminution of the two hand suspension. Both the individual and the group curves show a trend toward extinction of the reflex

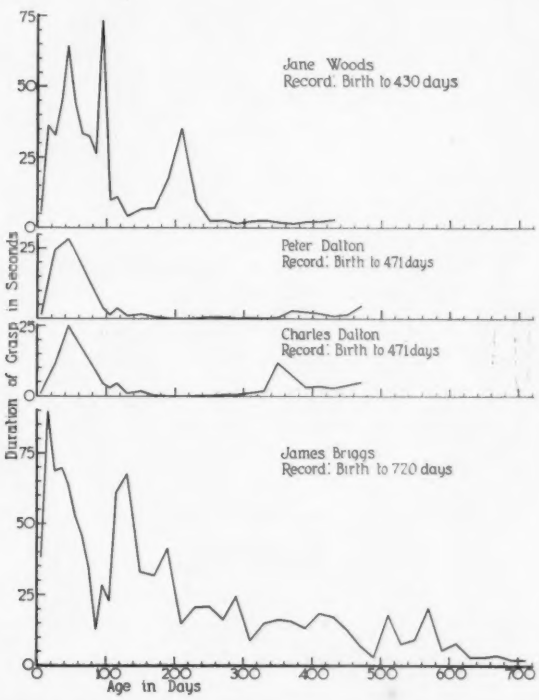


Fig. 4.—Curves showing two hand suspension time for 4 children, 2 of them identical twins. Note similarity in the curves for the twins.

phase similar to that previously observed in the decline of the Moro reflex.[4] This similarity suggests that the neural mechanisms controlling these two phylogenetic activities may be of the same order.

Crying is a component of the suspension behavior during the reflex phase. Curves showing the incidence of crying for 4 of the babies on whom daily observations were made are presented in figure 8.

4. McGraw, M. B.: The Moro Reflex, Am. J. Dis. Child. **54**:240-251 (Aug.) 1937.

It was also observed that certain significant postural adjustments accompanied changes in suspension time. It is difficult to know whether these neuromuscular changes are merely concomitant or whether they are an essential part of the suspension activity. During the early phase of two hand suspension the baby's head drops back toward the interscapular portion of the spine, while the lower extremities are flexed on

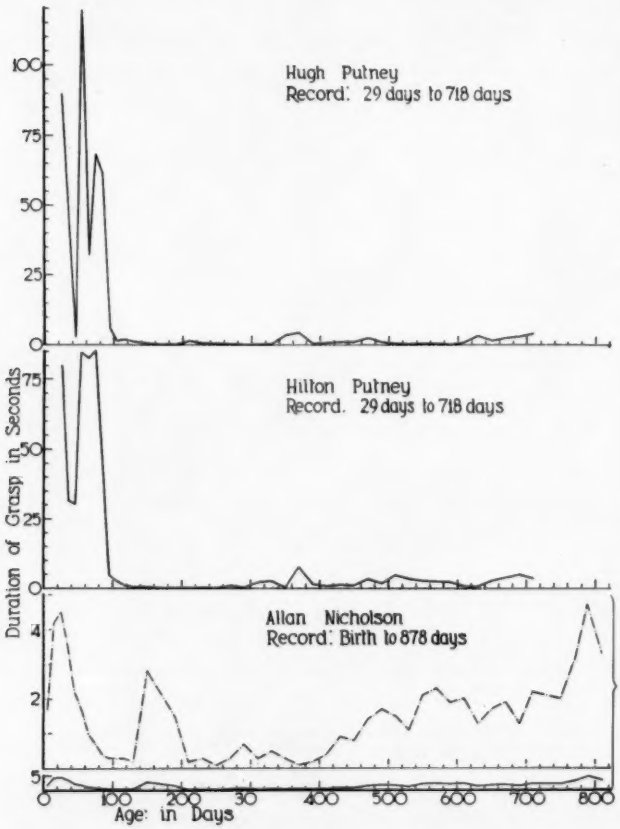


Fig. 5.—Curves showing two hand suspension time for 3 children, 2 of them identical twins. Note the similarity in curves for the twins. The curves for Allan Nicholson are drawn on two different ordinate scales.

the abdomen. As the baby grows older he tends to hold his head erect; extension increases in the lower extremities until finally they hang down straight (fig. 9). It has been observed that as older children become fatigued during suspension they often regress to a posture simulating that of the newborn infant, that is, they flex the legs on the abdomen and drop the head backward.

There are also developmental changes in the prehension of the rod. The grip of the newborn infant is localized primarily in the distal phalanges, while the thumb, adducted on the palm, plays an inactive role. As the child grows older there is an increasing tendency for him

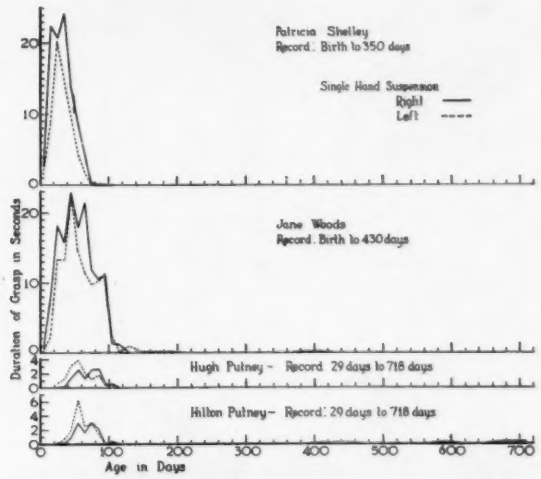
Patricia Shelley
Record: Birth to 350 days
Single Hand Suspension
Right
Left
Jane Woods
Record. Birth to 430 days
Hugh Putney - Record 29 days to 718 days
Hilton Putney - Record: 29 days to 718 days
Duration of Grasp in Seconds
Age in Days

Fig. 6.—Single hand suspension time for 4 children.

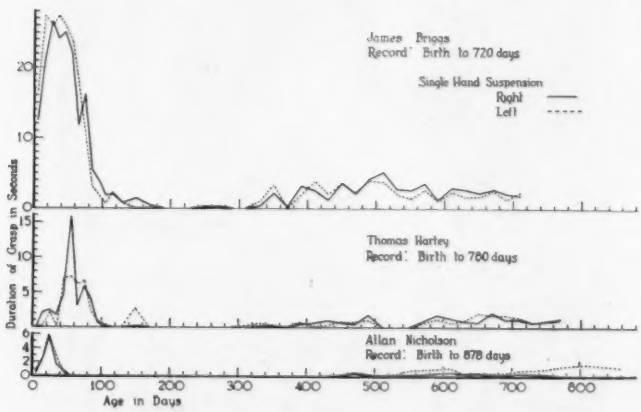


Fig. 7.—Single hand suspension time for 3 children.

to hold the rod in the palm of the hand with the thumb actively engaged in the grip. The change in manner of grip corresponds somewhat to the shift from reflex to deliberate grasping. This transition is further indicated by the child's refusal to grasp the rod at all when it is placed in his hand.

In all of the children on whom daily observations were made, reflex closure of the digits continued after single hand suspension had

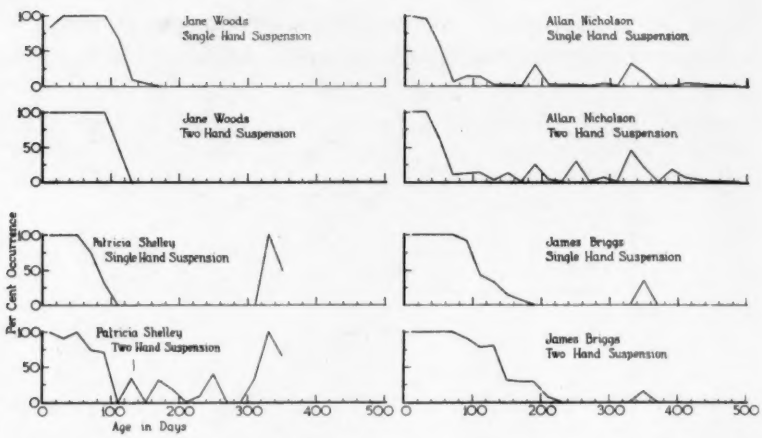


Fig. 8.—Curves showing the incidence of crying during suspension, indicating that it is common during the reflex phase.

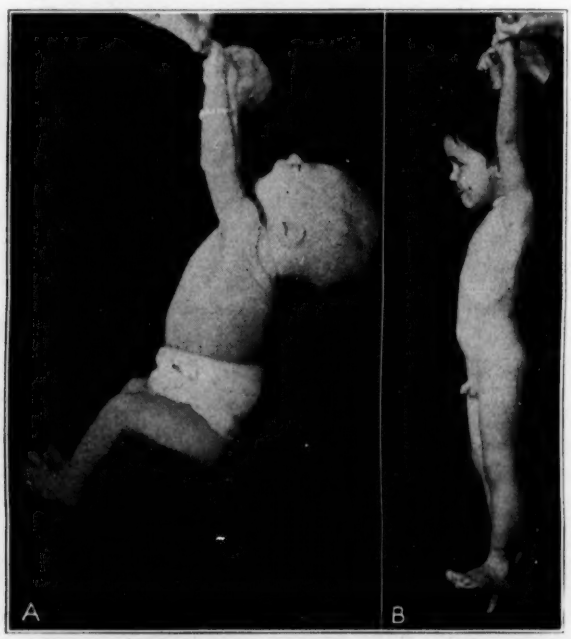


Fig. 9.—Photographs showing posture of children during suspension grasp behavior: *A*, reflex suspension of newborn infant; *B*, voluntary suspension of older child.

reached a zero level. This phenomenon is illustrated by the curves in figure 10, which show the incidence of suspension and of closure of the digits around the rod as obtained from daily observations of 1 infant during the first three hundred days of life. The disparity in the functioning of reflex suspension and reflex grasp lends support to the hypothesis that the two activities are of different phyletic origin.

Certain theoretic considerations also support the assumption that reflex closure and reflex suspension are of different phyletic origin. It appears that recent phylogenetic achievements are more specific in their ontogenetic manifestation than are the more ancient behavior patterns. The suspension phenomenon, as previously pointed out, is more definite in ontogenetic functioning than is the reflex closure of the digits. In fact, it is often difficult to locate the period of change from reflex to deliberate closure of the digits, but it is not difficult, because of its specificity, to determine the period of single hand suspension and its extinction. Furthermore, ancient phylogenetic archievements are com-

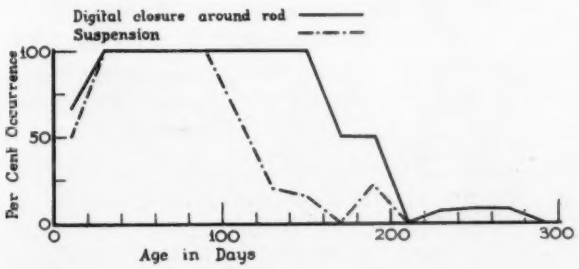


Fig. 10.—Curves showing the difference in 1 child between reflex suspension and reflex closure of the digits around a rod.

mon to a greater number of species than recent acquisitions. Reflex swimming movements,[5] for example, seem to be common to all vertebrates, including the human infant. There are many reasons to believe that swimming movements comprise one of the most ancient phylogenetic activities. Reflex closure of the digits in response to cutaneous or proprioceptive stimuli is also common to many species, but the ability to suspend the body by flexing the digits of the forelimbs around a rod appears to be peculiar to the primates, including man. On this basis, the reflex closure of the digits is considered a more ancient phyletic achievement than is the suspension phenomenon.

In summary, the significant changes in the development of the suspension ability of the infant and young child are as follows:

1. The ability to suspend the weight of the body is manifested in practically all newborn infants but does not attain its maximum strength

5. McGraw, M. B.: Swimming Behavior of the Human Infant, J. Pediat. **15**:485-490, 1939.

until about the end of the first month. After this maximum there occurs a rapid decline in suspension time until the ability becomes extinct or drops to a low level about the end of the fourth postnatal month.

2. The trend of the suspension activity is more clearly defined when measurements are made on single hand performances than on two hand suspension.

3. The ability to suspend the weight of the body is reestablished or reenforced toward the end of the first or the beginning of the second year. Qualitative differences indicate that this later behavior is of a different order from the suspension of the newborn infant.

4. Because of certain qualitative differences in ontogenetic manifestation, a distinction has been drawn between the reflex closure of the digits and the early suspension behavior, with the implication that the two phenomena are of different phyletic origin.

## INTERPRETATION

As Tilney [6] and Conel [7] have concluded from anatomic studies that the cerebral cortex is not functioning at birth, it is reasonable to assume that the suspension phenomenon at this age is controlled at a subcortical or lower level in the central nervous system. Indeed, one is forced to this assumption by the fact that the phenomenon is exhibited by anencephalic infants.[8] The lengthening of the suspension time during the first month gives no evidence of cortical activity; it may result from further development of lower neural centers and paths or from increasing muscular strength. The reduction in suspension time after the first month may be regarded as a sign that the inhibiting influence of the cortex is beginning to assert itself. This phase develops rapidly during the next three months. Cortical inhibition becomes completely dominant, and suspension behavior is either extinct or at a low level. Later, signs appear which indicate that the cortex is beginning to take over active control of behavior; and toward the end of the first year the activity becomes reestablished in a way which manifests a large degree of voluntary cooperation.

These theoretic considerations are in keeping with those proposed in connection with other studies [9] of neuromuscular development. The

6. Tilney, F.: The Structure and Development of the Brain, unpublished lecture.

7. Conel, J. L.: The Postnatal Development of the Human Cerebral Cortex, Cambridge, Mass., Harvard University Press, 1939, vol. 1, pp. 5-44.

8. I have observed this phenomenon in 3 anencephalic infants. It has also been observed by Watson.[3c]

9. McGraw, M. B.: Development of Neuro-Muscular Mechanisms as Reflected in the Crawling and Creeping Behavior of the Human Infant, J. Genetic Psychol., to be published.

earliest signs of cortical functioning, as observed in overt behavior, are in the nature of diminished nuclear or subcortical movements. Cortical inhibition is reflected not only by the reduction of reflex movements but also by the expansion of extensor development. It has also been observed in connection with other studies that the locus of primary extensor development is in the region of the cervical vertebrae, scapulas and humeri. These observations on the locus of early extensor development are supported by the results of Conel's [7] studies of neural structures, which indicate that most advanced structural development at birth is in the middle third of the posterior wall of the gyrus centralis anterior. This area is the one which controls movements of the trunk, upper extremities and head. Conel has also pointed out that those cells in the third quarter of the anterior central gyrus, counting from above toward the lateral fissure, are less well developed than those which control movements from the cervical portion of the spinal cord. The cells of this area control movements of the hands and digits. This observation of Conel is in harmony with observations on grasping behavior, which indicate that reflex closure of the digits is sustained longer than uninhibited reflex movements of the cervical portion of the spine, shoulder girdle and proximal segments of the upper extremities.

SUMMARY

This paper presents the results of a study of the suspension grasp behavior of a group of 91 infants and young children ranging in age from birth to 7 years, together with those from longitudinal studies of this activity in 8 individual children during the first year or more of life.

There are three distinct phases of this behavior: (1) the reflex phase, which extends over the first four months of life, (2) the transitional phase, when suspension time is at a low level, if present at all, and (3) the voluntary or deliberate phase, which appears around the beginning of the second year and continues during the ensuing years.

The reflex phase is controlled by nuclear or subcortical centers; the decline or extinction of the suspension phenomenon is interpreted as an indication of development in cortical cells, which exercise an inhibitory influence on subcortical functioning.

The recurrence or reenforcement of the ability to suspend the body is regarded as evidence of maturation in those cortical cells which activate or control neuromuscular movements and of their integration with neural centers which govern other factors involved in deliberate performances.

# HEMOLYTIC DISEASE IN INFANTS

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As hemolytic anemia manifests itself only rarely in early infancy and because the symptoms and progress differ when it does so appear, I have deemed it worth while to attempt to point out the essential features of this disease entity when seen at an early age.

In 1 of the 3 cases here reported symptoms were noted at birth, and in the other 2, at 4 months of age. In none of the 3 could a familial history be obtained.

The following descriptive terms for this condition have been noted in the literature: congenital acholuric jaundice; splenomegalic icterus, Hayem; congenital family cholemia; congenital hemolytic icterus; congenital hemolytic anemia, and congenital or familial hemolytic disease. The Minkowski-Chauffard type is the familial or congenital type; it was first classed as a clinical entity by Minkowski [1] in 1900, and in 1907 Chauffard [2] linked this condition with lowering of erythrocytic resistance. The Hayem type is the acquired type; it was first described by Hayem [3] in 1898.

In hemolytic disease of early infancy, anemia is often a more pronounced symptom than icterus and is generally severe. The onset of the illness in the young infant may occur as a severe hemolytic crisis and may terminate fatally. Diamond [4] recently reported such a case in a 6 month old infant. The changes in the blood in these infants are usually exaggerated, both as to size and as to shape of the red cells, and the percentage of nucleated and reticulated erythrocytes present may be high. Splenomegaly in these infants is usually of a considerable degree.

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Read before the Chicago Pediatric Society, Oct. 17, 1939.

1. Minkowski, O.: Ueber eine hereditäre, unter dem Bilde eines chronischen Icterus mit Urobilinurie Splenomegalie und Nierensiderosis verlaufende Affection, Verhandl. d. Kong. f. inn. Med. **18**:316, 1900.

2. Chauffard, A.: Pathogénie de l'ictère congénital de l'adulte, Semaine méd. **27**:25, 1907.

3. Hayem, G.: Sur une variété particulière d'ictère chronique splénomégalique, Presse méd. **1**:121, 1898.

4. Diamond, L. K.: Congenital Hemolytic Anemia in Infancy and Childhood, M. Clin. North America **21**:401 (March) 1937.

### CLINICAL AND LABORATORY DATA

The table lists in detail the clinical and laboratory data characteristic of hemolytic disease in infancy and indicates the findings in the 3 cases reported in this paper.

*Occurrence in Early Infancy.*—It has been stated in the literature that the first appearance of this condition in early infancy is rare,[5] and onset in the neonatal period has been infrequently recorded. It is probable, however, that if the condition were more often thought of many more instances would be reported. In a recent publication Diamond [4] stated that the first symptoms in 2 infants under his observation appeared at the ages of 2½ and 4 months. Debré [6] in reviewing 20 cases reported on a 4 month old infant in whom splenomegaly had been noticed in the newborn period. Parsons [7] recently reported on 2 cousins suffering from this condition, in 1 of whom the symptoms were first observed at 3 months of age. Josephs [8] noted 2 instances of first appearance in early infancy, in 1 of which symptoms may have been present at birth. Schiff [9] recently reported a case in which the first symptoms were present during the newborn period. In my cases the symptoms were first noted in 1 instance at birth and in the other 2 infants at 4 months of age.

*Onset.*—The onset may be insidious, or the disease may appear with terrifying suddenness and terminate fatally, as in the case reported by Diamond.[4] When the symptoms appear early, the first crisis is apt to be most severe. Such a severe crisis was noted in 1 of the cases here presented. In the other 2 infants there were frequent crises which, though not so severe, necessitated transfusions at intervals of from three weeks to three months.

*Familial Occurrence.*—The occurrence of this condition in cousins, mentioned by Parsons,[7] is the only instance in which a familial history has been noted when the disease occurred in early infancy. Debré [6] recently reviewed the occurrence in fourteen different families and expressed the belief that the condition is transmitted as a dominant

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5. Cooley, T. B.: The Anemias, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 16, p. 31.

6. Debré, R.; Lamy, M.; Sée, G., and Schrameck, G.: Congenital and Familial Hemolytic Disease in Children, Am. J. Dis. Child. **56**:1189 (Dec.) 1938.

7. Parsons, L. G.: The Hemolytic Anemias of Childhood, Lancet **2**:1395 (Dec. 17) 1938.

8. Josephs, H. W.: Studies in Hemolytic Anemia: I. Hemolysis, Compensatory Regeneration and Erythroblastosis, Bull. Johns Hopkins Hosp. **62**:25 (Jan.) 1938.

9. Schiff, E.: Congenital Hemolytic Anemia with Normal Fragility of the Red Blood Cells, Arch. Dis. Childhood **13**:264 (Sept.) 1938.

*Clinical and Laboratory Data in Three Cases of Hemolytic Disease in Infants*

| | Comment | Case 1 (S. G.) | Case 2 (L. D.) | Case 3 (P. H.) |
|---|---|---|---|---|
| First appearance | Rare in infancy; may be in form of crisis and end fatally | Sudden, at age of 4 months | Pale since birth | Yellow since birth |
| Familial history | May be present or absent | — | — | — |
| Jaundice | May be absent | Slight | Marked; noted at 4 mo.; thought due to carotinemia | Moderate, since birth |
| Anemia | Always present in infants | | | |
| | Red blood count | 790,000 | 2,225,000 | 1,830,000 |
| | Hemoglobin | 30% | 35% | 36% |
| | Color index | 1.3 to 1.8 | 1.1 | 1.3 |
| Changes in the blood | (a) Macrocytosis and spherocytosis may be present | Macrocytosis | Microcytosis; spherocytosis | Macrocytosis |
| | (b) Reticulocytosis always present | Reticulocytes, 35% | Reticulocytes, 25% | Reticulocytes, 34% |
| | (c) Erythrocytic fragility may be increased or decreased; normal or increased resistance does not rule out diagnosis | Partial hemolysis, 0.44%<br>Complete hemolysis, 0.34% | Partial hemolysis, 0.50%<br>Complete hemolysis, 0.42% | Partial hemolysis, 0.38%<br>Complete hemolysis, 0.28% |
| | (d) White blood count may be normal or increased | 6,700 to 11,900 | 10,000 to 17,000 | 8,750 |
| | (e) Platelets may increase after splenectomy | | | |
| | No. before operation | 160,000 to 190,000 | 310,000 | 160,000 |
| | No. after operation | (no operation) | 200,000 | 301,000 |
| | (f) Erythroblastemia; usually increased number of normoblasts | + | + | + |
| | (g) Bilirubinemia always present | + | + | + |
| | Ieteric index is increased | 27 | 19 | 36 |
| | Direct van den Bergh reaction is negative | — | — | — |
| | Indirect van den Bergh reaction is positive | + | + | + |
| Changes in bone marrow | Erythroblastic reaction: increase in number of nucleated red blood cells | + | None obtained | None obtained |
| Splenohepatomegaly | Always present | + | + | + |
| Occasional physical findings: | | | | |
| (a) General glandular enlargement | Occasionally present | — | — | — |
| (b) Skeletal changes | Absent in young infants | — | — | — |
| Febrile crisis | Occasionally occurs | + | — | — |
| Urine | Urobilin always increased | + | + | + |
| | Occasional hemoglobinuria | + | — | — |
| Stools | Acholia absent | Normal | Normal | Normal |
| Treatment: | | | | |
| (a) Temporary | Transfusion | + | + | + |
| | Serum | + | — | — |
| (b) Permanent | Splenectomy | Not performed | At age of 15 mo. | At age of 2½ yr. |

characteristic according to Mendel's law. No familial history could be traced in the 3 cases here reported.

*Jaundice.*—When the illness is first manifested in early infancy, jaundice may be entirely absent, even though there is indisputable evidence of a considerable increase in destruction of blood. The jaundice varies considerably from time to time and is most marked in a remission following a crisis. In 1 of the infants here reported on jaundice was slight, anemia being the striking feature. Jaundice was noted at birth in 1 of the infants and in the other 2 not until the fourth month.

*Anemia.*—Anemia is always one of the most striking features of the disease in young infants and may be severe. In 1 of my cases the number of red cells fell to 790,000, and the hemoglobin content similarly diminished. The color index is usually over 1.

*Findings in the Blood.*—It has been generally believed that one of the diagnostic criteria for this condition is the spherocytosis and microcytosis so commonly noted. Until recently the presence of microcytosis was, indeed, a criterion without which the diagnosis could hardly be made. However, it has now been recognized in older patients with this disease, and more particularly in infants, that neither microcytosis nor spherocytosis is prerequisite to this condition. Occasionally, as pointed out by Hill,[10] macrocytosis and spherocytosis may be present. The occurrence of macrocytosis surely cannot rule against the diagnosis. In the 3 cases here reported macrocytosis was twice noted, while microcytosis occurred only once. The tendency for macrocytosis to be more or less physiologic in the young infant probably accounts for the frequency here observed.

Reticulocytosis is a most characteristic feature of this condition. The increase in reticulocytes is considerable in young infants. In the 3 cases here reported the percentage of reticulocytes in the red blood counts averaged from 25 to 35. Baty [11] has recorded a case in which there were 92 per cent of reticulocytes in the peripheral blood.

Since the days of Chauffard,[2] increased fragility of the erythrocytes has been one of the outstanding criteria for the diagnosis of this condition. However, fragility may be normal or the resistance of the erythrocytes may be even somewhat increased. Debré [6] noted this fact, and Schiff [9] recently reported a typical case with normal fragility of the red blood cells. A normal or even an increased resistance does not rule out the diagnosis. In 1 patient here presented the erythrocytes

10. Hill, J. M.: Dimensions of the Red Cells in Familial Hemolytic Anemia, J. A. M. A. **111**:2179 (Dec. 10) 1938.

11. Baty, J. M.: Case of Congenital Hemolytic Jaundice with Unusually High Percentage of Reticulocytes, Am. J. M. Sc. **179**:546 (April) 1930.

showed an increased resistance, in 1 a normal resistance and in 1 a decreased resistance to hypotonic salt solution.

The white blood count is generally normal or somewhat increased. The number of platelets is usually within normal limits. Occasionally, a considerable rise in the number of platelets has followed splenectomy. A certain increase in the number of normoblasts is generally noted. In 1 of the cases here reported 36 normoblasts were found per hundred white blood cells counted.

Bilirubinemia is always present. The icteric index is increased, and the indirect van den Bergh reaction is positive. In all of the cases here reported there were the usual changes in the blood.

*Changes in the Bone Marrow.*—Smears of the bone marrow obtained by sternal puncture reveal an increased number of nucleated erythrocytes. Instead of the normal 15 per cent, 50 per cent or over have been noted in this condition. This hyperactivity of the bone marrow is characteristic of hemolytic disease.

In 1 of the 3 infants in this series on whom sternal puncture was performed, a great increase in the number of nucleated erythrocytes of the bone marrow was noted; they constituted approximately 70 per cent of the nuclear elements in the smear.

*Splenohepatomegaly.*—In all cases the spleen is enlarged. When the disease appears in early infancy, the enlarged spleen may extend below the umbilicus and completely fill the left flank. There was considerable enlargement of the spleen in all 3 cases here reported. The liver may also show considerable enlargement, and this feature was noted in my cases. Both spleen and liver are usually firm to the touch on palpation.

*Occasional Physical Findings.*—Occasionally, there may be general glandular enlargement in older patients, but this is not usually observed in early infancy and was not present in the infants here reported on.

Cardiac murmurs, which are probably so-called hemic murmurs due to anemia, have been noted.

Difficulties in development and infantilism have been reported, as well as skeletal deformities.[12] However, these occurrences are due to the chronicity of the disease and would not be expected in infants suffering from the condition. There were no skeletal changes in my 3 patients. The association of gallstones with this condition has been occasionally reported.[13]

In older patients ocular lesions may occur, but they have not been reported in infancy.

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12. Gänsslen, M.; Sipperten, E., and Schüz, E.: Neue deutsche Klin. (supp. 4) **14**:607, 1936.

13. Gairdner, D.: Association of Gall-Stones with Acholuric Jaundice in Children, Arch. Dis. Childhood **14**:109 (June) 1939.

*Febrile and Hemolytic Crises.*—The crises which characterize the course of this disease may show varying degrees of severity and different manifestations. Generally, the infant manifests prodromal symptoms, such as lassitude, lack of appetite and fretfulness, followed by deepened jaundice and increased anemia. Usually during these periods of crisis the spleen enlarges and the urine becomes dark. Abdominal symptoms have not been characteristic of the condition in infancy.

Occasionally, crises are initiated by febrile attacks, and all the symptoms are magnified, and the infant may be extremely prostrate. When fever accompanies the crisis anemia is most severe. Periodicity in the occurrence of these hemolytic crises is the rule. The interval between crises varies considerably. In 1 of the infants here reported on a crisis occurred every three weeks, in another approximately every three months and in the third a single severe crisis occurred.

The extent of jaundice and anemia during a single crisis in the same patient will vary considerably from attack to attack.

*Character of Urine and Stools.*—The amount of urobilin in the urine is increased, especially after a crisis. Occasionally hemoglobinuria may be noted; this occurred in 1 patient here reported on during a crisis. The stools are normal but occasionally dark. Acholia is never present.

*Treatment.*—The best temporary treatment after a crisis is transfusion. In an acute crisis, when anemia is so severe that there is danger of anoxemia and insufficient blood volume, frequent small transfusions must be resorted to, though the transfused blood seems to be much more rapidly hemolyzed when given during a crisis than when given during an interval between crises.

Blood serum has been recommended, and 1 patient here reported on besides receiving transfusions during the crisis also received 200 cc. of human serum in doses of 20 cc. over a period of several weeks.

The only permanently successful type of therapy is splenectomy. This operation was inaugurated by Banti in 1903 for this condition.[6] Although the operation carries with it a certain risk, it seems wise to urge that it be performed even in early infancy. The normal growth and development of the infant after operation, as well as the prevention of certain skeletal and developmental complications which occur during the chronic course of the disease, seem more than to counterbalance the operative risk.

It would seem well to advise the operating surgeon to search for any possible accessory splenic tissue at the time the spleen itself is removed. It has been occasionally reported that improvement followed splenectomy for a time and then symptoms returned. On second operation an accessory spleen, greatly hypertrophied, has been removed. Permanent

success, therefore, depends on removal not only of the spleen but of any accessory splenic tissue.

After operation, certain changes occur, some of which have already been noted. The crises cease. Jaundice lessens and usually disappears entirely. Occasionally, a subicteric tinge remains, which is especially noted in the scleras. Anemia rapidly improves, and the blood picture generally returns to normal. The reticulocyte count gradually drops to normal. Rarely, the platelet count rises, sometimes to a marked degree, but it usually subsides to within the normal range after a time. Occasionally, microcytosis and somewhat increased fragility of the red cells persist after operation. The increased signs of hemolysis quickly disappear after splenectomy.

The spleen was removed from 2 of the infants here reported on. In 1 patient the operation was performed at the age of 15 months. Signs of hemolysis rapidly subsided, and the blood count steadily rose to a normal level. The reticulocyte count gradually fell to normal, as did the number of normoblasts. Fragility of the red cells became less marked, and microcytosis and spherocytosis persisted, though they were not as pronounced as before splenectomy.

In the second infant splenectomy was performed at the age of 2½ years. This child had had a history of jaundice and anemia since birth, and crises occurred at approximately three month intervals, at which times transfusions were required. After operation, the anemia improved rather promptly, though the hemoglobin level has always remained somewhat lower than normal. The red cells vary between 2,500,000 and 3,500,000, and the hemoglobin content between 50 and 65 per cent. A slight icteric tinge is still noted in the scleras, more marked at some times than at others. This child had a considerably enlarged liver, which, after operation, gradually decreased in size but is still palpable after two years. Physical growth has been rapid since splenectomy, and the general health has been good. This infant had had macrocytosis; the size of the red blood cells has since returned to normal. The fragility of the red cells was increased rather than decreased before operation. When last tested fragility was approximately normal. This infant would have been operated on at an earlier age had the parents consented. The persistence of slight icterus and anemia, together with the enlarged liver, probably points to the fact that hemolytic foci persist in some other organs. There have been no crises since the operation, and there is no reason to suspect that accessory splenic tissue has developed, as such tissue was carefully looked for at the time of operation. No additional attempts, such as by transfusion or parenteral injection of liver extract, have been made to bring the red blood count and hemoglobin content up to what would otherwise be considered normal, as the development, growth and activity

of the child, now 4½ years old, seem in no way impaired; in fact, he is unusually large and active for his age.

Diamond and Blackfan [14] in reporting cases of hypoplastic anemia have similarly noted that children suffering from this condition have been able to adjust themselves to low hemoglobin levels and red blood counts without impairing their physical or mental growth.

*Differential Diagnosis.*—In the newborn hemolytic anemia must be differentiated from physiologic icterus, anemia of the newborn, erythroblastosis foetalis, sepsis and congenital syphilis. Congenital obstruction of the bile ducts and congenital hepatic cirrhosis will cause jaundice but not anemia of the hemolytic type. In the neonatal period early manifested sickle cell anemia, or Cooley's disease, might cause some difficulty in differentiation. When the progress of such an illness is followed and the recurring crises are noted the differentiation of this disease is not too difficult. The only other condition in which increased fragility of the red blood cells has been noted is in poisoning with toluenediamine.

## COMMENT

Until the cause of this type of hemolytic anemia is established, the condition must be grouped with the other hemolytic anemias of unknown etiology. As Parsons [7] has pointed out for this group in general, the question which must be answered in these conditions resolves itself into the conundrum of whether the abnormality is to be found in the blood serum or in the erythrocytes. Is the erythrocyte itself more liable to injury or more fragile than the normal erythrocyte, or are the red blood cells normal and the serum abnormal, in that it contains hemolysins, lacks antihemolysins or contains abnormal constituents derived from chemical products or toxins from infection?

A $p_H$-labile lysin has been demonstrated in normal serum which would be capable of producing hemolysis of abnormal erythrocytes.[15]

Josephs and Wincour [16] postulated a lack of some substance normally present in plasma in these cases of hemolytic anemia. They observed a temporary reduction in the destruction of blood after transfusion, and expressed the belief that they had isolated this lacking essential in the ether-soluble fraction of concentrated protein-free plasma.

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14. Diamond, L. K., and Blackfan, K. D.: Hypoplastic Anemia, Tr. Am. Pediat. Soc. **50**:20, 1938.

15. Dacie, J. V.; Israels, M. C. G., and Wilkinson, J. F.: Paroxysmal Nocturnal Haemoglobinuria of Marchiaform Type, Lancet **1**:479 (Feb. 26) 1938.

16. Josephs, H. W., and Wincour, P.: Studies in Hemolytic Anemia: II. The Presence of an Anti-Hemolytic Factor in Human Plasma, Bull. Johns Hopkins Hosp. **62**:53 (Jan.) 1938.

Finally, it has been noted that lipolecithin may produce spherocytosis when experimentally administered, and it has been postulated that lysolecithin formed from the lecithin in the blood serum may produce hemolysis in this type of anemia.[17] It would seem from the therapeutic value of splenectomy that normally the spleen must have some regulatory power over the production of such abnormal hemolysins and in this condition must be incapable of supplying certain substances which might be termed antihemolysins.

In those cases ushered in by an acute hemolytic crisis, one may first be in doubt whether one is dealing with a first attack of hemolytic anemia or with the type of acute hemolytic anemia described by Lederer. Parsons [7] recently stated that he had observed the latter condition in the neonatal period, though he mentioned that the age is usually above 6 months.

Debré [6] remarked that in his opinion conditions diagnosed as acute hemolytic anemia of the Lederer type turn out after careful study to be hemolytic crises in patients suffering from congenital hemolytic disease. He stressed the fact that final diagnosis of the Lederer type of anemia should be made only if in the subsequent course no further attack occurs.

Gairdner [13] recently pointed out that these two types of acute hemolytic anemia may be indistinguishable during a crisis. Levy and Miller [18] recently reported a Lederer type of anemia in a 25 month old infant; the child had been suffering from infection prior to the hemolytic crisis and responded rapidly to transfusion. The considerable leukocytosis noted probably reflected the part played by infection in the production of the hemolytic crisis. Rapid recovery after transfusion is one criterion in the diagnosis of Lederer's type of anemia. The consensus in the literature seems to be that congenital hemolytic anemia is often incorrectly diagnosed as hemolytic anemia of Lederer's type.

## CONCLUSION

The various criteria, both clinical and laboratory, for the diagnosis of acute hemolytic anemia in infancy are not as clearcut as for the manifestation of the disease in the older child or the adult. Splenomegaly is the one constant finding in infants. Anemia is probably more marked in young children and jaundice less severe than in older patients. A red blood count of less than 1,000,000 cells is cause for considerable

17. Dameshek, W., and Schwartz, S. O.: Experimental Production of Various Types of Hemolytic Syndromes by Hemolytic Sera with Especial Reference to Spherocytosis, Increased Fragility Test and Reticulocytosis, J. Clin. Investigation **17**:501 (July) 1938.

18. Levy, W., and Miller, M. J.: Acute Hemolytic Anemia, Am. J. Dis. Child. **58**:349 (Aug.) 1939.

alarm in a 4 month old infant, and that a fatal outcome is not unlikely in such a crisis has been pointed out. Although transfusion in the crises has been said to be a life-saving measure, the hemolytic process at times is exaggerated by this procedure.

The condition is said to be rare in early infancy, though probably more and more instances at an early age will be reported in the future. When the onset is abrupt, in the form of a hemolytic crisis in the neonatal period, the diagnosis is not at once easily established. In such a circumstance, the clinical picture is often more helpful than the laboratory findings. It may be emphasized that the presence of microcytosis and spherocytosis, especially in an initial crisis, is not the rule. Increased erythrocytic fragility need not be present in these infants in order to make the diagnosis. High reticulocyte counts and an increased number of nucleated red blood cells are helpful but not diagnostic of the condition. Signs of increased hemolysis must be ascertained to make the diagnosis.

Blood transfusion and the administration of serum are temporary therapeutic aids which may be effectively used in combating an acute crisis. Splenectomy is to be recommended as a permanent therapeutic measure, and the benefits to be expected outweigh the hazards of the operation. Accessory splenic tissue should be searched for and removed at the time of operation. Of the 3 patients here reported on 2 have successfully undergone splenectomy at the ages of 15 months and 2½ years respectively.

## REPORT OF CASES

CASE 1.—S. G., a 4 month old boy, was admitted to the Sarah Morris Children's Hospital, service of Dr. I. Harrison Tumpeer, with a history of anorexia and lassitude for three days. The mother noted that the baby appeared pale and slightly ill. The family history was irrelevant. No members of the paternal family were known to have suffered from jaundice; information about the maternal relatives was lacking.

*Physical Examination.*—The patient was well developed, rather apathetic and listless, with extreme pallor accentuated by a greenish yellow tinge to the skin. The scleras showed a slight icteric tinge. There was no glandular enlargement. The heart rate was rapid, and no cardiac enlargement could be made out. A soft systolic murmur was best heard at the apex. The spleen was considerably enlarged and firm; the splenic notch was easily felt. The edge of the liver could be palpated 2 fingerbreadths below the costal margin.

*Laboratory Data.*—The red blood cells numbered 790,000 per cubic millimeter; the hemoglobin content was 30 per cent; the color index was 1.8; the leukocytes numbered 11,900 and the platelets 160,000. Stained smears revealed 35 per cent reticulocytes and a moderate poikilocytosis; the erythrocytes were chiefly macrocytes. The icteric index was 27. A test of fragility to hypotonic saline solution showed partial hemolysis at 0.44 per cent, complete at 0.34 per cent. The cholesterol

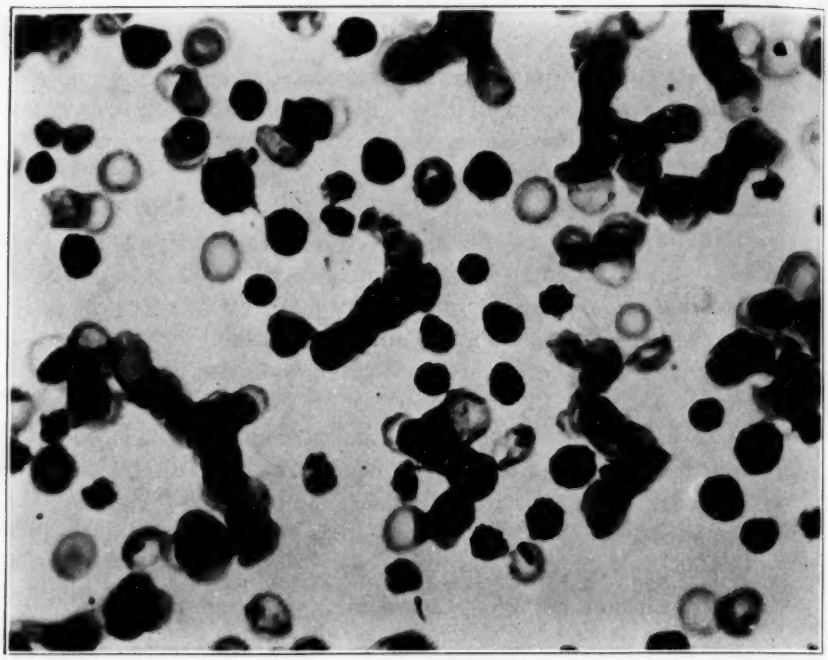

Fig. 1 (case 1).—Specimen of bone marrow obtained by sternal puncture, showing increased number of normoblasts and normoblastic nuclei; 70 per cent nucleated erythrocytes; × 160.

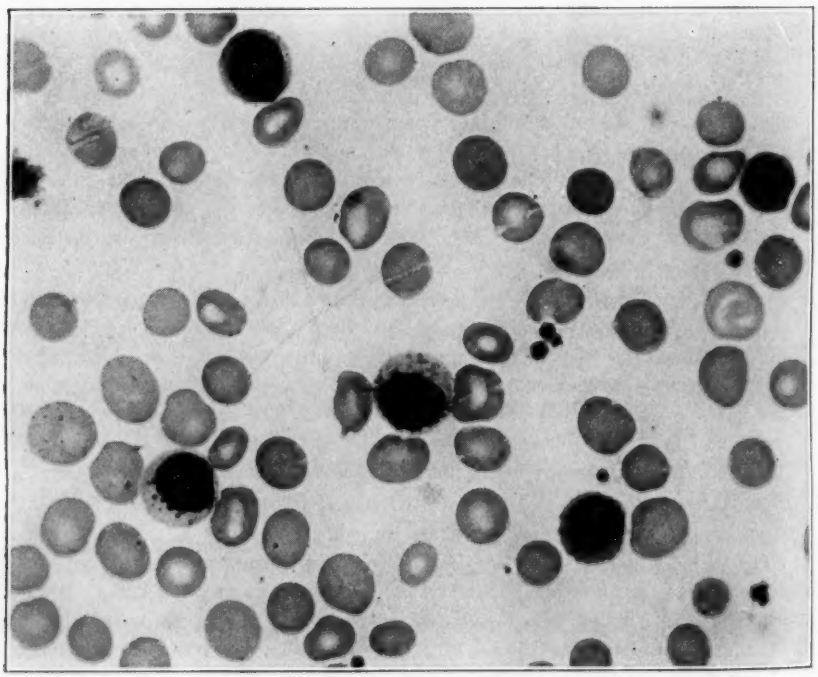

Fig. 2 (case 1).—Blood smear, showing macrocytosis. Wright's stain; × 160.

content of the blood was 135 mg. per hundred cubic centimeters. The Kahn and tuberculin skin tests were negative. Roentgenograms of the long bones and skull were normal.

*Course.*—The patient received five transfusions of blood during the first thirteen days in the hospital. On several occasions the nurses noted that the diapers were blood stained after urination, probably from hemoglobinuria. The amount of hemoglobin and the number of red cells increased after transfusion, but the red blood count dropped again in a few days to below 2,000,000. Approximately 100 cc. of blood was administered at each transfusion. The infant was given 20 cc. of human convalescent serum every second day until 200 cc. had been administered. A sternal puncture revealed 70 per cent nucleated erythrocytes in the bone marrow.

After the first two weeks of illness the temperature subsided to normal and a slow gain in weight was noted. The enlargement of the spleen subsided, but this organ was still palpable four months after the initial illness. The red blood count and hemoglobin level slowly returned to normal. Ten months after the acute onset, the spleen is no longer palpable and the blood count is apparently normal. There has been no recurrent crisis during the ten months following the initial attack, and no splenectomy has been performed.

CASE 2.—L. D., a 1 year old girl, had a normal history of birth. The child was well for the first five months, with the exception of occasional vomiting after feedings. At 9 months of age cereal and vegetable feedings were added to the diet; shortly thereafter the mother noticed that the baby's skin was rather yellow and waxy. She consulted her family physician, who attributed this appearance to the "excessive ingestion of carrots." The color did not disappear, however, when carrots were eliminated from the diet. No family history of jaundice could be discovered. The child crawled poorly and made no effort to stand.

*Physical Examination.*—The conjunctivas and the mucous membranes of the mouth were abnormally pale. The liver was palpable 3 to 4 cm. below the right costal margin. The edge of the spleen which reached below the umbilicus was palpable. A pink staining of the diaper was attributed to uric acid.

*Laboratory Data.*—The test for urobilin in the urine was positive, as was the indirect van den Bergh reaction. The icteric index was 19. There was a slight decrease in fragility to hypotonic saline solution (partial hemolysis at 0.56 per cent and complete at 0.42 per cent). The erythrocytes numbered 2,225,000, leukocytes 10,800, platelets 310,000 and reticulocytes 25 per cent. The hemoglobin content was 35 per cent. The red blood cells showed definite spherocytosis and microcytosis. The serologic and tuberculin tests were negative.

*Course.*—Injections of whole blood intravenously raised the red cell count to 3,420,000 and the hemoglobin content to 50 per cent, but they fell again to as low as 2,160,000 and 40 per cent respectively. The patient's appetite was good, but there was a slight loss of weight. After splenectomy by Dr. James Patejdl, the weight was regained and symptoms disappeared. A blood transfusion was given immediately after the operation. Eleven days later the erythrocyte count was 4,120,000 and the hemoglobin content 83 per cent. The infant was followed in the outpatient department and was perfectly well two years after operation. The blood count and hemoglobin content remained at normal levels; the reticulocyte count was normal. The fragility of the erythrocytes returned to normal, and growth and development have been excellent.

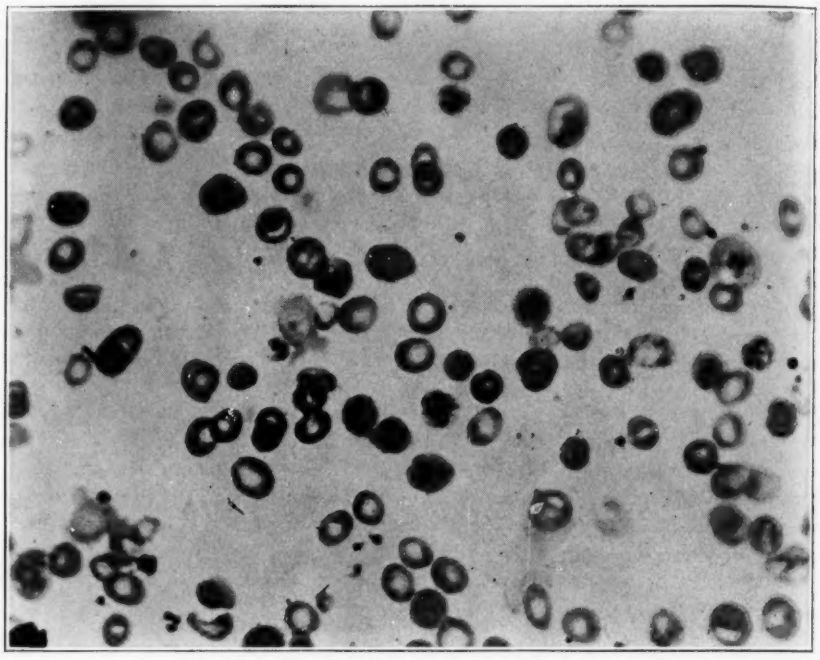

Fig. 3 (case 2).—Blood smear, showing microcytosis, spherocytosis and reticulocytosis (25 per cent) ; × 160.

Fig. 4 (case 2).—Patient L. D., before splenectomy.

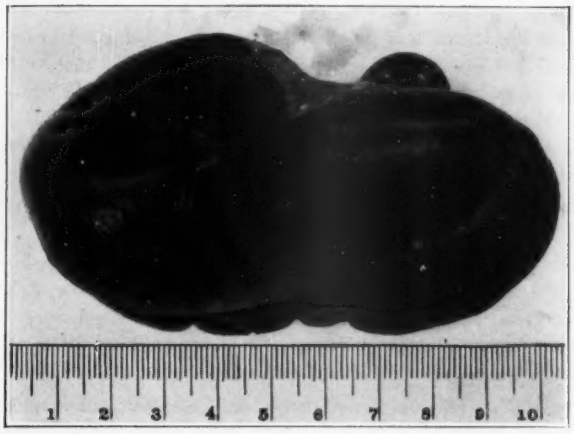


Fig. 5 (case 2).—Spleen immediately after removal.

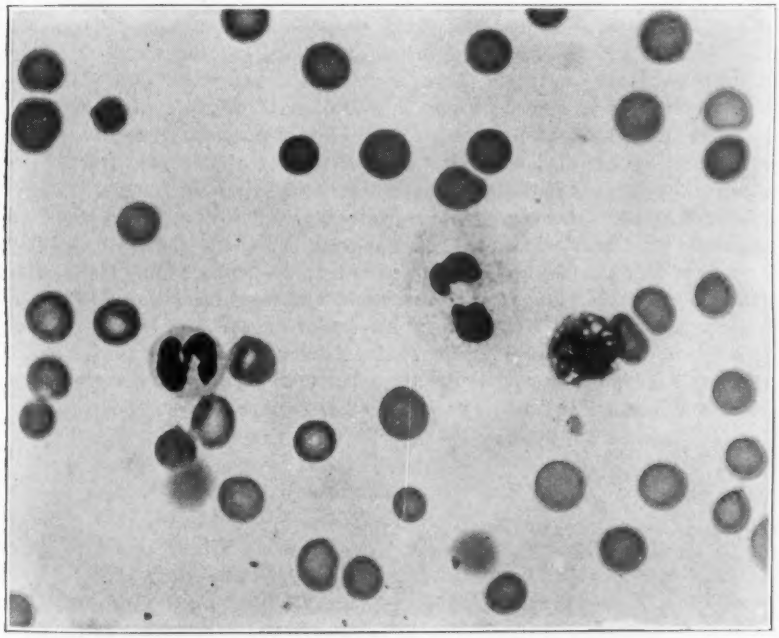

Fig. 6 (case 3).—Blood smear, showing macrocytosis; × 160.

CASE 3.—P. H., a boy was first seen at the age of 1 year. There was no known history of familial jaundice. It was noted by the obstetrician at the time of delivery that the infant was pale. A slight jaundice developed in the newborn period and had persisted; the history of jaundice in this case, therefore, dates from birth. At 4 months of age the red blood cell count was 1,500,000. Enlargement of the spleen was noted at this time, and since then cyclic deepening and regression of the jaundice had occurred. When anemia became marked at any time, the child was "dizzy, became nauseated and vomited." Hemolytic crisis occurred approximately every three months. In two years prior to operation the child had about fifteen transfusions.

*Physical Examination.*—Examination showed a moderate icteric tinge of the conjunctivas and pale mucous membranes. Enlargement of the liver and spleen was noted; both were palpable 3 fingerbreadths below the costal margin. The spleen had a sharp, firm edge and was fairly narrow; it was enlarged to four or five times normal size.

*Laboratory Data.*—The red blood count was 1,830,000; the hemoglobin content was 36 per cent; erythrocytic fragility was increased (partial hemolysis at 0.38 per cent and complete hemolysis at 0.28 per cent). The platelets numbered 160,000 leukocytes 8,750 and reticulocytes 34 per cent. The icteric index was 36. The indirect van den Bergh reaction and the test for urobilin were positive. The red blood cells were nearly all of the macrocytic type and remained so during the one and a half years the infant was followed before splenectomy. There was an increased resistance of the erythrocytes to hypotonic salt solution on repeated tests during this interval.

*Course.*—Splenectomy was performed when the child was 2½ years of age by Dr. James Patejdl. After operation the red blood cell count rose to 3,700,000 and the hemoglobin content to 65 per cent. In the two years since splenectomy the erythrocytes have ranged between 2,500,000 and 3,000,000 and the hemoglobin content between 60 and 65 per cent. The number of normoblasts and reticulocytes has returned to normal, and the last test of fragility of the red blood cells was normal. The liver had gradually decreased in size, and the general health has been excellent. At times a slight jaundice and subicteric tint to the scleras have been noted. The icteric index is within normal limits, and the urine is negative for urobilin. Growth and development have been pronounced since the operation, and at 4½ years the measurements for height and weight are considerably above the average. The boy is active and no longer has the spells of lassitude observed before operation. No special attempts have been made to correct the persisting anemia, and it should be noted that there has been no interference with normal growth, development and activity with this low erythrocyte level and hemoglobin value. He is in perfect health.

104 South Michigan Avenue.

# BLOOD VOLUME AND EXTRACELLULAR FLUID VOLUME OF INFANTS AND CHILDREN

## STUDIES WITH AN IMPROVED DYE MICROMETHOD FOR DETERMINATION OF BLOOD VOLUME

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A method for the determination of brilliant vital red in plasma has been described previously by one of us.[1] In the present study we have attempted to show that the method is simple and accurate, that it may be used for determination of blood volume and that it dispenses with the use of expensive equipment necessary for methods more recently advocated.[2] We have used the method in order to gain some information on "mixing time" and the disappearance of brilliant vital red from the blood stream. Later, we have applied some of this experience in clinical research on children.

### METHOD

Standard solutions were made up in heparinized whole blood drawn immediately before injection of the dye. (Heparin does not affect the hematocrit reading.) Sufficient brilliant vital red was added to produce a concentration close to that of the calculated unknown. The dye, usually 10 mg. per kilogram of body weight,[3] was injected intravenously, and a sample of blood was drawn after three or four minutes. From 0.05 to 0.10 cc. of serum or plasma and 1 cc. of 95 per cent alcohol were pipetted into a small tube and were mixed by shaking. The tubes

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From the Department of Pediatrics and the Department of Physiology and Pharmacology, University of Georgia School of Medicine.

1. Hamilton, W. F.: Some Mechanisms Involved in the Regulation of the Circulation, Am. J. Physiol. **102**:551, 1932.

2. (*a*) Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937. (*b*) Gregersen, M. I.; Gibson, J. G., and Stead, E. A.: Plasma Volume Determination with Dyes; Errors in Colorimetry; Use of the Blue Dye T-1824, Am. J. Physiol. **113**:54, 1935.

3. Such large doses are nontoxic but frequently cause some staining of the skin which lasts for several days.

were centrifuged, and the clear supernatant fluids were compared in a microcolorimeter.

The blood volume may be calculated by the following formula:

$$BV = \frac{I}{C_U}, \quad C_U = \frac{C_S \cdot R_S}{R_U}$$

in which BV equals blood volume in liters; I, milligrams of injected dye; $C_S$, concentration of standard in milligrams per liter; $C_U$, concentration of unknown in milligrams per liter; $R_S$, colorimeter reading of standard, and $R_U$, colorimeter reading of unknown. Accurate weighing of the dye is unnecessary since only the ratio $\frac{C_S}{I}$ is used for the calculation.

The plasma volume and the cell volume may be calculated from the hematocrit reading. Objections have been raised to estimating whole blood volumes by the dye method since the hematocrit reading of capillary blood may differ from that of venous blood in larger vessels.[4] However, we feel that information on whole blood volume is of greater interest in most clinical investigations than the knowledge of plasma volume and that the error in calculating whole blood volumes is probably small and a fairly constant fraction.

In order to show the usefulness of the method we had to prove (1) that alcohol does not greatly decrease the intensity of color of brilliant vital red, (2) that the precipitated proteins do not absorb excessive amounts of the dye, (3) that the dye in the supernatant fluid is always a constant fraction of the total dye present in the sample, (4) that turbidity and adventitious color are sufficiently well removed from the solution to permit perfect color matches over the range of concentrations usually encountered (± 30 per cent). In addition, we had to show the limitations of the method, i. e., with respect to the amount of plasma protein and hemoglobin that can be removed by alcohol precipitation.

## EXPERIMENTAL WORK

*Experiment 1.*—Solutions of brilliant vital red of 1:5,000 concentration in water and in 95 per cent alcohol were compared colorimetrically. The watery solution was found to be 3 per cent stronger. The small difference is insignificant since the color match was not perfect.

*Experiment 2.*—This experiment showed how much dye is absorbed by the precipitated proteins. The following solutions were compared colorimetrically:[5]

| Solution | Colorimeter Reading |
|---|---|
| Standard (0.05 cc. of BVR [1:5,000] + 0.95 cc. of 95 per cent alcohol) | 20.0 |
| Unknown (0.05 cc. of BVR [1:5,000] + 0.90 cc. of 95 per cent alcohol + 0.05 cc. of plasma [6]) | 31.2 |

4. (*a*) Smith, H. P.; Arnold, H. R., and Whipple, G. H.: Blood Volume Studies: VII. Comparative Values of Welcker, Carbon Monoxide and Dye Methods for Blood Volume Determinations; Accurate Estimations of Absolute Blood Volume, Am. J. Physiol. **56**:336, 1921. (*b*) Gregersen, M. I., in McLeod, J. J. R.: Physiology in Modern Medicine, ed. 8, St. Louis, C. V. Mosby Company, 1938, p. 912.

5. All colorimeter readings in this report are the arithmetical means of 10 or more individual readings.

6. The supernatant fluid of the centrifuged specimen was used here as in all other subsequent mixtures of alcohol and plasma.

The color match is poor, but a rough intensity match shows that approximately one third of the dye is absorbed by the precipitate.

Solutions containing less dye than the foregoing samples (concentrations in the colorimeter cups 1:100,000) are difficult to match. Protein precipitants other than alcohol have not been found practical. Trichloracetic acid and many others precipitate all the dye with the proteins.[1] Acetone evaporates too rapidly. Neither have other dyes been proved useful. Seventy-five per cent of the blue dye T-1824 is precipitated by alcohol. Many other dyes formerly used have been abandoned since they leave the blood stream too rapidly.[7]

*Experiment 3.*—This experiment was performed in order to show that the dye in the supernatant fluid is a constant fraction of the total dye in the sample. Various dye solutions in plasma were made up. Identical samples were treated with alcohol or diluted with corresponding volumes of water:

Samples 1 to 6 were composed of 0.05 cc. of plasma plus 0.05, 0.06, 0.07, 0.08, 0.09 and 0.10 cc. of brilliant vital red (1:5,000) plus sufficient alcohol to make up 1 cc. samples. Samples 7 to 12 consisted of identical solutions of brilliant vital red in plasma plus sufficient water to make up 1 cc. samples. Solutions 2 to 6 were compared with solution 1 as standard; solutions 8 to 12 were compared with solution 7 as standard:

| Solutions | Expected Readings | Observed Readings | Solutions | Observed Readings |
|---|---|---|---|---|
| Standard (1) | .... | 20.0 | Standard (7) | 20.0 |
| 2 | 16.7 | 16.6 | 8 | 16.7 |
| 3 | 14.3 | 14.4 | 9 | 14.5 |
| 4 | 12.5 | 12.5 | 10 | 12.6 |
| 5 | 11.1 | 11.2 | 11 | 11.1 |
| 6 | 10.0 | 9.8 | 12 | 9.9 |

The results show that the solutions made up with alcohol yield accurate results, even if the unknown solution is twice as concentrated as the standard. Blood volumes rarely differ by more than 25 per cent from their estimated value, and standard solutions can be made up accordingly close to the unknown.

Experiments similar to the preceding one were carried out with markedly lipemic plasma. No color matches could be obtained with watery solutions because of their opacity. The samples made up with alcohol were perfectly transparent and the colorimeter readings were as accurate as in the absence of lipemia. Alcohol apparently dissolves the neutral fats and fatty acids while the alcohol-insoluble lipoids are precipitated with the proteins.

*Experiment 4.*—Partial hemolysis of a blood sample occurs not infrequently. By the use of the original colorimetric method it was impossible to distinguish between the red color of the dye and of the hemoglobin.

A solution of hemoglobin was prepared by hemolyzing one part of red blood cells with 9 parts of distilled water. Varying amounts of this solution (0.03 to 1 cc.) were added to 1 cc. of plasma. The plasma plus hemoglobin was treated as before with 20 parts of alcohol. The supernatant fluids appeared clear and colorless on inspection unless more than 0.2 cc. of the solution of hemoglobin was added.[8] The removal of hemoglobin is dependent on the presence of plasma. Watery solutions of hemoglobin alone cannot be cleared up by treatment with alcohol.

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7. Gregersen, M. I.: An Analysis of Colorimetric Methods in Relation to Plasma Volume Determinations, J. Lab. & Clin. Med. **23**:423, 1938.

8. This corresponds to hemolysis of approximately 5 per cent of the cells in a blood sample.

*Experiment* 5.—In the following experiment we compared readings of solutions made up with alcohol with those of watery solutions in the determination of brilliant vital red in plasma containing hemoglobin.

The standard solution consisted of 0.05 cc. of normal plasma plus 0.05 cc. of brilliant vital red (1:5,000). Unknown solution 1 consisted of 0.05 cc. of plasma containing 0.33 per cent hemolyzed erythrocytes plus 0.05 cc. of brilliant vital red. Unknown solution 2 consisted of 0.05 cc. of plasma containing 0.66 per cent hemolyzed erythrocytes plus 0.05 cc. of brilliant vital red. The colorimetric readings of these solutions follow:

| Solutions Mixed With Alcohol | | Watery Solutions | |
|---|---|---|---|
| Standard | 20.0 | Standard | 20.0 |
| Unknown 1 | 19.8 | Unknown 1 | 17.8 |
| Unknown 2 | 19.35 | Unknown 2 | 15.1 |

In most experiments of this kind the error due to hemoglobin has been reduced 85 to 90 per cent. Such reductions make the error in most cases negligible. Samples containing much hemoglobin appeared entirely clear on inspection of the tubes but were frequently somewhat brownish when seen through the colorimeter. Such samples were easily recognized, because the precipitated proteins at the bottom of the tube appeared brown instead of pink. Samples should be discarded if turbidity is severe enough to prevent a good color match. This is rarely necessary if blood samples are treated with reasonable care.

Accurate determination of the injected dye is complicated if the plasma was colored before the injection. The color may be due to residual dye from previous injections or to the natural color of the plasma, to bilirubin or other pigments. Two methods of correction for residual dye may be used.

1. Two standards of different strength are made up from plasma containing residual dye and are read against each other. The concentration of residual dye may be calculated from the formula:

$$\frac{C_r + C_1}{C_r + C_2} = \frac{R_{s2}}{R_{s1}}, \qquad C_r = \frac{R_{s2} C_2 - R_{s1} C_1}{R_{s1} - R_{s2}}$$

in which $C_r$ equals concentration of residual dye in milligrams per liter; $C_1$, concentration of added dye in first standard in milligrams per liter; $C_2$, concentration of added dye in second standard in milligrams per liter; $R_{s1}$, colorimeter reading of first standard, and $R_{s2}$, colorimeter reading of second standard.

The concentration of the unknown sample ($C_U$), giving the colorimeter reading $R_U$ if read against the first standard, is calculated from

$$\frac{C_r + C_1}{C_r + C_U} = \frac{R_U}{R_{s1}}, \qquad C_U = \frac{R_{s1}\,(C_r + C_1)}{R_U} - C_r$$

The blood volume, as given previously, equals $\frac{I}{C_U}$

For example, if I equals 250 mg., $C_1$, 100 mg per liter; $C_2$, 200 mg. per liter; $R_{s1}$, 20; $R_{s2}$, 12, and $R_U = 16$, then

$$C_r = \frac{(12 \cdot 200) - (20 \cdot 100)}{20 - 12} = 50 \text{ mg. per liter.}$$

$$C_U = \frac{20\ (50 + 100)}{16} - 50 = 137.5 \text{ mg. per liter.}$$

$$BV = \frac{250}{137.5} = 1.82 \text{ liters.}$$

Disregard of the residual dye would have given a blood volume 10 per cent too high.

This method, in principle, has been advocated previously.[9] The calculations used here are slightly different. It is advisable to compare in all cases standards of different strength to exclude the presence of extraneous color or of any contamination.[9] Smith has employed a different method of correcting for residual dye (Smith [10] and Gregersen [7]). His method requires the comparison of dye solutions varying widely in concentration. Its application requires relatively high concentrations of residual dye and the use of undyed plasma. These difficulties are eliminated by our method.

2. The other method used in correcting for residual dye is the use of the compensating colorimeter (fig. 1). Gregersen [11] has been unable to obtain accurate results with the compensating colorimeter. Using this instrument, we have

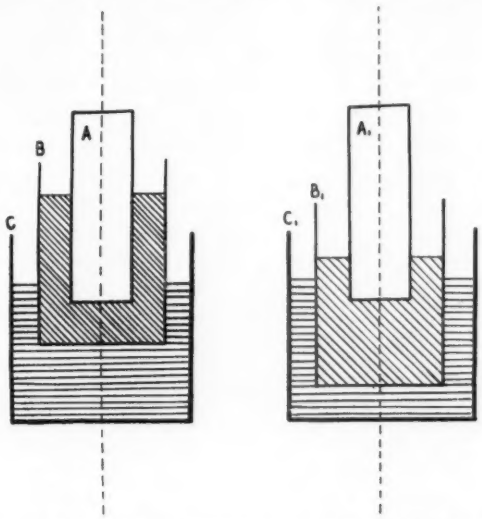


Fig. 1.—Compensating colorimeter (Bausch and Lomb). $A$ and $A_1$, indicate fixed plungers; $B$ and $B_1$, small cups containing the solutions to be compared, and $C$ and $C_1$, larger cups containing the compensating solution (plasma containing residual dye or bilirubin). $B$ and $B_1$ can be moved separately, and $C$ and $C_1$ can only be moved together. The distance between the plungers and the bottom of the larger cups is identical on both sides. The light traverses, therefore, equal depths of residual dye (or bilirubin) irrespective of the position of the smaller cups. The small additional cups of the instrument, used for $p_H$ determinations, are not necessary for determinations of blood volume.

9. Hamilton, W. F.; Moore, J. W.; Kinsman, J. M., and Spurling, R. G.: Studies on the Circulation: IV. Further Analysis of the Injection Method and of Changes in Hemodynamics Under Physiological and Pathological Conditions, Am. J. Physiol. **99**:534, 1932.

10. Smith, H. P.: Blood Volume Studies: II. Repeated Determinations of Blood Volume at Short Intervals by Means of the Dye Method, Am. J. Physiol. **51**:221, 1920.

11. Gregersen (footnotes 4 *b* and 7).

been able to determine accurately added dye in solutions made up in plasma containing residual dye or bilirubin. Alcohol was used in preparing the solutions for all four cups. The only important advantage of spectrophotometric or photoelectric analysis appears to be the use of lower concentrations of dye. Staining of the skin is common with our method if determinations of blood volume are repeated frequently over a short period of time.

Both principles may be used in a heterochromatic system (brilliant vital red and bilirubin or other pigments).

(*a*) With the use of a properly selected color filter, matches may be obtained in monochromatic light. The calculations are identical with those reported for residual dye.

(*b*) With a certain amount of training it is possible to obtain intensity matches without a color filter or with an imperfect filter. The calculations are the same as those given for residual dye. It is admittedly poor colorimetry, but experiments have convinced us that if the extraneous color is weak and if the concentration of the unknown is close to that of the standard, the errors are small enough for the method to be used if special equipment is not available.

*Experiment* 6.—We have used the compensating colorimeter (fig. 1) in all cases in which extraneous color was present. A typical example is the following:

Solution for the large cups
0.6 cc. of icteric serum + 11.4 cc. of 95 per cent alcohol
Solution for the small cups
Left cup—0.2 cc. of icteric serum + 0.2 cc. of brilliant vital red (1:5,000) + 3.6 cc. of 95 per cent alcohol
Right cup—0.2 cc. of icteric serum + 0.4 cc. of brilliant vital red (1:5,000) + 3.4 cc. of 95 per cent alcohol

| | | |
|---|---|---|
| Colorimeter readings... | L. 20.0 | |
| No compensation..... | R. 11.2 | 12 per cent error (rough intensity match) |
| With compensation.... | R. 10.1 | 1 per cent error (perfect color match) |

It is essential for the solutions in all four cups to be perfectly transparent. The samples should be discarded if the color match is not perfect.

*Experiment* 7.—The proportion of plasma to alcohol should be the same in all samples whenever alcohol is used. This is illustrated in the following experiment in which solutions 1 to 5 were compared with the standard.

| Solution | Colorimeter Readings |
|---|---|
| Standard (0.02 cc. of plasma + 0.07 cc. of BVR [1:5,000] + 1.01 cc. of alcohol)..... | 20.0 |
| Sol. 1 (0.04 cc. of plasma + 0.07 cc. of BVR [1:5,000] + 0.99 cc. of alcohol)..... | 21.4 |
| Sol. 2 (0.06 cc. of plasma + 0.07 cc. of BVR [1:5,000] + 0.97 cc. of alcohol)..... | 20.5 |
| Sol. 3 (0.08 cc. of plasma + 0.07 cc. of BVR [1:5,000] + 0.95 cc. of alcohol)..... | 19.7 |
| Sol. 4 (0.10 cc. of plasma + 0.07 cc. of BVR [1:5,000] + 0.93 cc. of alcohol)..... | 18.6 |
| Sol. 5 (0.12 cc. of plasma + 0.07 cc. of BVR [1:5,000] + 0.91 cc. of alcohol)..... | 17.0 |

The supernatant fluid of all samples was perfectly clear. However, it frequently became cloudy if the plasma exceeded 10 per cent and always became turbid if it exceeded 20 per cent of the mixture. The color matches in this series were poor and became progressively worse with increasing concentrations of plasma. The errors were due to several factors:

1. With larger amounts of plasma more alcohol-soluble plasma pigments were added to the red dye.

2. Larger amounts of plasma apparently do not absorb much more dye. The precipitate in the first two samples was intensely pink; it became progressively paler in the samples containing more plasma.

3. In this experiment, the same amount of brilliant vital red was dissolved in increasingly smaller amounts of weaker alcohol.

*Experiment* 8.—Information concerning extracellular fluid was desirable in many experiments on blood volume. From the concentration of sodium sulfocyante in plasma one or two hours after intravenous injection, one may calculate the volume of diluting or "available" fluid.[12] This figure has been shown[13] to be a fair approximation to the volume of extracellular fluid. A 6.5 per cent solution of sodium sulfocyanate was injected slowly in doses of 15 to 20 mg. per kilogram of body weight. Chemical determinations were carried out according to the method of Crandall and Anderson.[12a] Sodium sulfocyanate and brilliant vital red can be determined in the presence of each other. The color of brilliant vital red does not interfere with the colorimetric determination of sodium sulfocyanate, since the dye is completely precipitated by trichloroacetic acid. The solutions must be injected separately, since strong solutions of electrolytes precipitate the dye. Renal excretion of sodium sulfocyanate during the one or two hour period is variable but rarely exceeds 1 per cent for two hours. Specimens of urine could not be collected from many small children. In these instances we corrected arbitrarily for an excretion of 1 per cent in two hours.

It seemed interesting to compare the disappearance from the plasma of brilliant vital red and sodium sulfocyanate. In dogs anesthetized with morphine sulfate both external jugular veins were exposed. Brilliant vital red and sodium sulfocyanate were injected simultaneously. The injection required approximately ten seconds. Samples of blood were taken from a cannula in the femoral artery. The cannula emptied into small tubes attached to a slowly rotating drum. Samples were obtained every five seconds for one and one-half to two minutes. Later samples were taken at longer intervals from the jugular vein.

Figure 2 represents a typical experiment. Both substances appeared in the femoral artery soon after injection. The concentration of both substances reached a peak simultaneously (mean time for circulation from neck to leg: approximately ten seconds), decreased and began to rise again when recirculation started (approximately one and one-half times the period necessary for complete circulation after the injection). The concentration of dye fell, first rapidly, later more slowly. Fluctuations in the concentration of the dye usually disappeared one minute after the injection. The shape of the disappearance curve suggests to us that mixing of the dye is complete after two to three complete circulations. We do not feel that the disappearance of dye during the first few minutes is due to slow mixing as suggested by others.[2a] It is more easily explained by diffusion of some of the dye into the lymphatics (Smith[14]). This process should be more rapid at first for obvious reasons. The concentration of successive samples plotted

12. (*a*) Crandall, L. A., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate, Am. J. Digest. Dis. & Nutrition **1**:126, 1934. (*b*) Gregersen, M. I., and Stewart, J. D.: Simultaneous Determination of the Plasma Volume with T-1824 and the "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142, 1939.

13. Lavietes, P. H.; Bourdillon, J., and Klinghoffer, K. A.: The Volume of Extracellular Fluid of the Body, J. Clin. Investigation **15**:261, 1936.

14. Smith, H. P.: Intravenous Injections of Fluid and Repeated Blood Volume Determinations, Bull. Johns Hopkins Hosp. **37**:177, 1925.

against time should and actually does give a curved and not a straight line. Figures for blood volume will be smaller if this fact is taken into consideration and will approach more closely the values obtained by the carbon dioxide method.

The sulfocyanate while passing through the pulmonary circulation was dissolved in a volume of fluid approximately equal to the blood volume (sulfocyanate enters the red blood cells[15]). But when the sulfocyanate returned from the systemic circulation it was diluted by a volume of fluid becoming progressively larger for thirty to ninety minutes. This curve also fails to show irregular fluctuations after a "mixing time" of approximately one minute.

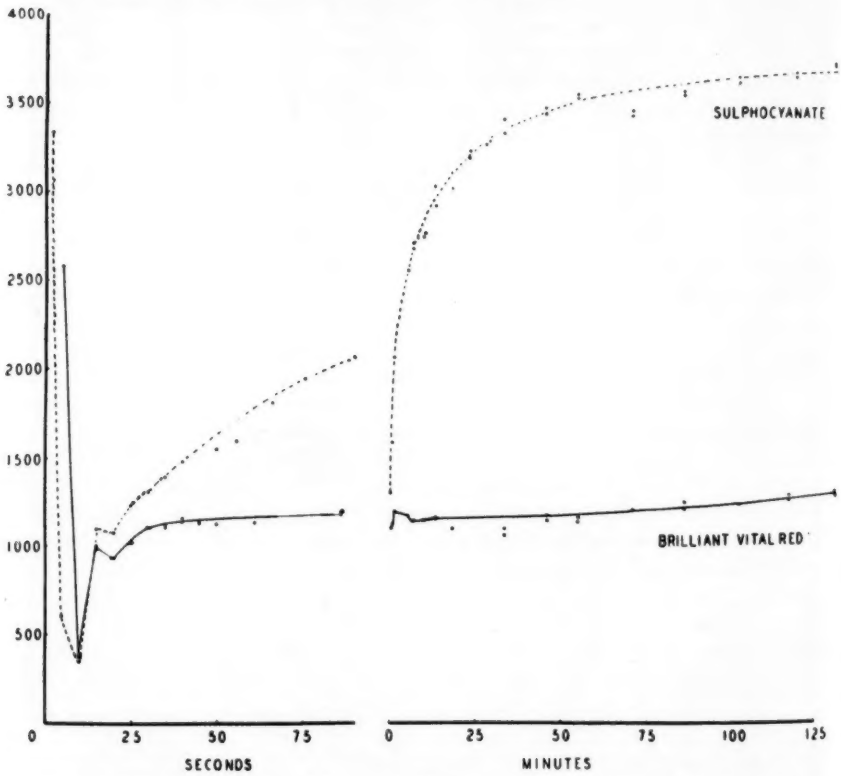


Fig. 2.—Chart showing mixing and disappearance of brilliant vital red (continuous line) and sodium sulfocyanate (dotted line). The abscissas represent the time (seconds on the left diagram and minutes on the right diagram), and the ordinates, reciprocals of plasma concentrations or apparent volume of blood available for the dilution of the substances.

## CLINICAL INVESTIGATION

*Newborn Infants.*—We have determined the blood volume of 20 normal newborn infants between the ages of 1 hour and 10 days. We found the total blood volume rather uniform, the mean 98.3, $\sigma =$

15. Gregersen and Stewart.[12b] Lavietes, Bourdillon and Klinghoffer.[13]

± 8.7 cc. per kilogram of body weight, somewhat higher than later in life. The hematocrit readings were high and quite variable (mean 52.7 ± 7.1). High blood volumes were slightly more common with high hematocrit readings.

On studying our figures we were surprised to find an inverse relation between the hematocrit reading and the plasma volumes (fig. 3 *A*). A similar phenomenon has recently been reported by Gibson [16] for the changes in blood volume during specific therapy for pernicious anemia: Total blood volumes increased only slightly, red cell volumes increased markedly, while plasma volumes decreased.

Our findings may be explained as follows: Immediately after delivery the uterus squeezes blood from the placenta into the infant.

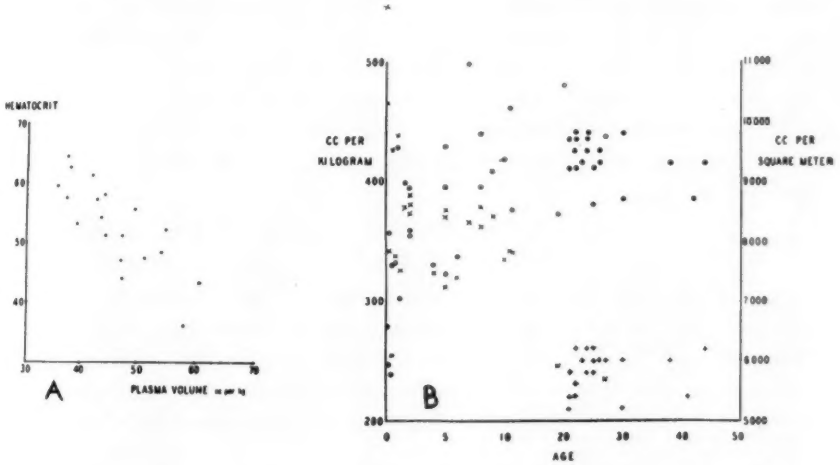


Fig. 3.—*A*, relation between relative plasma volume and hematocrit reading in newborn infants. The ordinates represent cubic centimeters of plasma volume per kilogram of body weight, and the abscissas, the hematocrit readings. *B*, relation between extracellular fluid volume and age, body weight and body surface. The abscissas represent age in years, and the ordinates, extracellular fluid volumes per kilogram of body weight (crosses) and per square meter of body surface (circles). The data for adults, vertical crosses and solid circles are values published by Crandall and Anderson.[12a]

The amount of blood received by the infant will vary with the strength of uterine contractions, with the time elapsed before the tying of the umbilical cord and, perhaps, with the activity of the infant's respiration. The weight of the newborn infant may increase more than 100 Gm.

16. Gibson, J. G., Jr.: Clinical Studies of the Blood Volume: VI. Changes in Blood Volume in Pernicious Anemia in Relation to the Hematopoietic Response to Intramuscular Liver Extract Therapy, J. Clin. Investigation **18**:401, 1939.

before the cord is tied [17] (3 per cent of the body weight; 37.5 per cent of a blood volume calculated as 80 cc. per kilogram of body weight).

The infant's circulation has probably a limited capacity, and total blood volume is regulated within narrow limits rather than plasma volume. Presumably, the infant loses at first water or whole plasma from the blood stream. The excess of cells is removed later by hemolysis. This mechanism alone does not explain the polycythemia and the icterus of the newborn period, but we believe that it contributes to the explanation.

We have found in the literature only one study on the subject. Lucas and Dearing [18] in 1921 reported the blood volumes of 30 newborn children. They found blood volumes less uniform and much higher than in our group (mean 147 $\pm$ 25 cc. per kilogram). In their series blood volumes were calculated from plasma volumes and the hematocrit readings. The high hematocrit readings (57.7 $\pm$ 5.8) suggest that their blood samples were incompletely centrifuged and the resultant blood volumes consequently too high. However, their plasma volumes were also considerably higher than ours. The plasma of all newborn infants is definitely icteric. Failure to correct for extraneous color may explain some of the peculiar results.

*Older Infants and Children.*—We determined the blood volume and "extracellular fluid volume" [19] simultaneously for some 30 older infants and children chosen from a pediatric ward. The volumes of children showing obvious dehydration or edema were analyzed separately. However, many of the other children were moderately anemic, malnourished or convalescent from infections and could not be considered normal. A group of healthy normal children would probably show more uniform results.

The figures on blood volume do not differ considerably from those found by previous investigators.[20] High plasma volumes were more commonly found associated with high extracellular fluid volumes, although this relation was not constant. A close correlation has been reported in dogs.[12b]

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17. Budin, P.: A quel moment doit-on pratiquer la ligature du ucordon ombilical? Progrès méd. **3**:750 and 765, 1875; **4**:2 and 36, 1876; Obstétrique ea gynécologie, Paris, O. Doin, 1886, pp. 1-35. Schücking: Zur Physiologie der Nachgeburtsperiode, Berl. klin. Wchnschr. **5**:18, 1877.

18. Lucas, W. P., and Dearing, B. F.: Blood Volume in Infants Estimated by the Vital Dye Method, Am. J. Dis. Child. **21**:96 (Jan.) 1921.

19. The term extracellular fluid volume is used throughout this article. It is emphasized again that the figures so calculated are not identical with but closely related to the true volume of extracellular fluid.

20. Darrow, D. C.; Soule, H. C., and Buckman, T. E.: Blood Volume in Normal Infants and Children, J. Clin. Investigation **5**:243, 1928.

Extracellular fluid volumes were calculated on the basis of actual and ideal weight [21] and of body surface and were related to age. The data plotted in the diagram (fig. 3 *B*) show that the extracellular fluid volumes increase with age if calculated on the basis of body surface but decrease if calculated on the basis of body weight. The latter agrees with Gregersen's findings in dogs.[12b] The results are not surprising in view of the following facts: Total body water and chloride (extracellular water) are very high in the fetus and decrease progressively with age, while fetal potassium (intracellular water) increases slightly.[22] The relatively small extracellular fluid volumes in relation to body surface may help to explain why infants and young animals become so easily dehydrated.

*Extracellular Fluid Volumes Under Abnormal Conditions*

| Time Determinations Made at Age of | Weight in Kg. | | "Extracellular" Fluid Volume | | | | |
|---|---|---|---|---|---|---|---|
| | Actual | Ideal | Cc. | Cc. per Kg. Actual Weight | Cc. per Kg. Ideal Weight | Cc. per Sq. M. | Comment |
| 5 mo. | 9.51 | 7.75 | 2,412 | 254 | 311 | 5,770 | Very fat infant |
| 6½ mo. | 5.00 | 7.77 | 2,128 | 426 | 274 | 7,600 | Malnourished infant |
| 27 yr. | 71.82 | 54.26 | 16,850 | 235 | 311 | 9,730 | Obese woman |
| 70 yr. | 44.32 | 69.77 | 23,470 | 530 | 336 | 16,080 | Extremely emaciated woman * |
| 8 wk. | 3.18 | 4.82 | 1,394 | 438 | 289 | 6,900 | Pyloric stenosis; dehydration |
| 2 hr. later | .... | .... | 1,585 | ... | ... | ..... | Determinations made after subcutaneous injection of physiologic solution of sodium chloride |
| 11 wk. | .... | .... | 1,746 | 541 | ... | 8,120 | Determinations made after pyloroplasty; nutrition poor |
| 15 wk. | .... | .... | 1,637 | 418 | ... | 6,820 | Nutrition improved |
| 2 yr. | 11.43 | .... | 4,940 | 432 | ... | 9,790 | Acute glomerular nephritis; moderate edema |
| 3 wk. later | 10.23 | .... | 3,880 | 380 | ... | 8,090 | No edema |
| 8 yr. | 35.23 | .... | 16,890 | 479 | ... | 14,560 | Acute glomerular nephritis; marked edema |
| 1 wk. later | 28.67 | .... | 10,360 | 341 | ... | 9,770 | No edema |

* This patient was operated on a few days later. Approximately 1,000 cc. of free fluid was found in the peritoneal cavity. The patient did not have edema.

It was found that the extracellular fluid volumes were very high for malnourished children and low for obese subjects. That was true even if the figures were calculated on the basis of body surface, as shown in the accompanying table. The same was found to be true in adults. This finding may be explained by two facts: 1. Fat tissue contains very little water. 2. Water in the gastrointestinal tract, available for the

21. Simmons, K., and Todd, T. W.: Growth of Well Children: Analysis of Stature and Weight; Three Months to Thirteen Years, Growth **2**:93, 1938.

22. Hamilton, B., and Dewar, M. M.: The Relation Between Water and Dry Substance in the Body of the Rat, Before and After Birth, Growth **2**:13, 1938. Stearns, G.: The Mineral Metabolism of Normal Infants, Physiol. Rev. **19**: 415, 1939.

dilution of sodium sulfocyanate,[12a] constitutes a larger fraction of the extracellular fluid volume in malnourished than in obese subjects.

Considerable spread of the values for each age group is noticed in the diagram (fig. 3 *B*). The extreme values fall closer to the mean of each age group if they are calculated on the basis of ideal instead of actual weight.[21] The mean extracellular fluid volume per kilogram of body weight is probably 10 to 20 per cent lower for normal children, since the majority of our subjects were 10 to 20 per cent underweight for their age and stature. Variations of extracellular fluid volume due to the nutritional state may obscure the effect of age (as mentioned previously) and of dehydration and edema, as shown in the following case:

An 8 week old infant was brought to the hospital because of persistent vomiting for two to three weeks. This child weighed 3.18 Kg., slightly below its birth weight. It looked emaciated, and the skin was dry and wrinkled. The lips and the tongue were dry, and the anterior fontanel was depressed. A diagnosis was made of hypertrophic pyloric stenosis with resultant malnutrition and dehydration. At this time the blood volume was 254 cc. and the extracellular fluid volume 1,394 cc., as shown in the table. Two hundred cubic centimeters of physiologic solution of sodium chloride was injected subcutaneously and another sample of blood was taken one hour later. At this time the extracellular fluid volume was 1,585 cc., i. e., 49.8 cc. per kilogram of body weight.

The child was operated on and ceased vomiting, but large amounts of isotonic fluids had to be administered daily to combat apparent dehydration. Three weeks later blood volume and extracellular fluid volume were determined again. At this time the child appeared fairly well hydrated. The extracellular fluid volume had increased considerably (to 1,746 cc.) while the weight had not changed, indicating some destruction of body tissue and its replacement by water (307 cc.).

The child began to take more food, and parenteral administration of fluid was soon discontinued. Another determination was done four weeks later. The extracellular fluid volume had decreased to 1,637 cc. while the body weight had increased to 3.92 Kg. The child looked better hydrated than ever before. The increase of body tissue must have been larger than one would have expected from the change in weight alone (gain of weight, 688 Gm.; loss of extracellular fluid volume, 109 cc.).

Two observations on this case appear of particular interest:

1. The 200 cc. of subcutaneously injected physiologic solution of sodium chloride was almost completely "available" for the sulfocyanate. Apparently little fluid had gained access to the circulation within one hour and could not, therefore, be transported to the cells. Definite local swelling at the site of injection confirmed this view. In other experiments[23] fluid was injected intravenously. One hour later a certain fraction of this fluid was found not to be "available." This fraction had presumably entered the cells.[12b]

Dehydration and malnutrition are commonly found combined in diseases of infants. The clinical manifestations, wrinkling of the skin, hollowness of the orbits and the type of facial expression, may be similar.

23. Experiments on dehydrated puppies carried out with Dr. R. A. Woodbury.

Acetonemia may be present in both conditions. On the other hand, edematous children may resemble obese ones. We have often found considerable edema at autopsy when a clinical diagnosis of dehydration had been made. Our patient was apparently slightly edematous at a time when he appeared still somewhat dehydrated, as shown in the table. We hope that similar serial determinations of extracellular fluid volume may lead to better evaluation of clinical signs (or the discovery of new ones) which will allow a more reliable estimation of hydration. This is of particular importance for the treatment of infants. The clinical appearance is usually the only guide for the parenteral administration of fluid, since it is often technically difficult to follow accurately the fluid intake and output in infants.

The occurrence of some very high figures for extracellular fluid volume raised the question whether under certain conditions some ions, as for instance $SCN^-$, might enter cells other than erythrocytes and certain glandular epithelial cells.[12a] This possibility has been suggested [24] in view of the finding of $Na^+$ in erythrocytes of nephrotic children [25] and of certain findings in nephritis.[26] This possibility throws the same doubt on the interpretation of studies of the excretion of base.[24]

The occurrence of such a condition would force an entirely different interpretation of our figures and even of the term "extracellular fluid volume." The functional difference between extracellular and intracellular fluid disappears when intracellular fluid becomes "available" for the dilution of sodium, chloride and sulfocyanate, therewith serving purposes usually reserved for extracellular fluid.

We felt that, short of death, severe shock would be the trauma most likely to change the permeability of cells to sulfocyanate. We injected sulfocyanate intravenously into dogs anesthetized with morphine sulfate. Approximately three hours later severe shock (low blood pressure and rapid pulse) was produced by single or repeated intravenous injection of 5 mg. of histamine phosphate. Plasma samples were taken at thirty minute intervals. No appreciable changes in the disappearance curve of sulfocyanate following the injection of histamine were observed in 4 experiments.

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24. McKay, E. M., and Butler, A. M.: Studies of Sodium and Potassium Metabolism: The Effect of Potassium on the Sodium and Water Balance in Normal Subjects and Patients with Bright's Disease, J. Clin. Investigation **14**:922, 1935.

25. Davison, W. C., and Salinger, R.: Tubular Nephritis (Nephrosis) in Children and Its Relationship to Other Forms of Nephritis, Bull. Johns Hopkins Hosp. **41**:329, 1927.

26. Blum, L., and Grabar, P.: Composition minérale des organes d'un sujet normal, Compt. rend. Soc. de biol. **101**:715, 1929; Teneurs des organes en Na et Cl dans l'urémie, ibid. **101**:717, 1929; Teneur des organes en chlore et en sodium chez des néphritiques appauvris en sel, ibid. **101**:718, 1929.

Two cases of acute glomerular nephritis with edema were studied. In both cases determinations (shown in the table) were done while the patient was edematous and after the edema had disappeared. The treatment during this time consisted of rest in bed only. No drugs were given; neither protein, salt nor water was restricted. It is apparent from the table that the changes in the extracellular fluid volume agreed surprisingly closely with the changes in body weight. The changes in plasma volume were less marked but in the same direction. These results seem to indicate that the edema in acute nephritis is entirely extracellular. The same conclusion has been reached for cardiac edema [12a] by similar methods and for the edema in certain types of chronic Bright's disease from data obtained from studies of base excretion.

## SUMMARY

A modified dye method employing brilliant vital red for the determination of blood volume is described. Ten to 20 volumes of 95 per cent alcohol are added to 0.05 to 0.10 cc. of plasma in order to remove proteins, lipoids, hemoglobin and other coloring or opaque matter. The clear supernatant fluids of centrifuged samples are compared in a microcolorimeter.

Methods are described by which brilliant vital red may be determined in the presence of residual dye and of extraneous color. Experiments in vitro show that the errors encountered are not larger than those reported for spectrophotometric methods.

Experiments on mixing time suggests that mixing of the dye in the blood stream is complete within ninety seconds.

Blood volumes of newborn infants averaged $98.3 \pm 8.7$ cc. per kilogram of body weight. The relative plasma volumes varied inversely with the hematocrit reading. A tentative explanation for this phenomenon is given.

"Extracellular fluid volumes" were calculated from the dilution of intravenously injected sodium sulfocyanate. These volumes increased with age if calculated on the basis of body surface but decreased if calculated on the basis of body weight.

Extracellular fluid volumes were found to be large in nephritic edema and in malnutrition. Low values were found in obesity and in dehydration.

Histamine shock in dogs did not change the concentration of sulfocyanate in plasma.

The fluid of edema in acute nephritis is apparently entirely extracellular.

# PARANASAL SINUSES FROM BIRTH TO LATE ADOLESCENCE

## II. CLINICAL AND ROENTGENOGRAPHIC EVIDENCE OF INFECTION

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The literature on sinusitis in infancy and childhood is far too voluminous to review in a few pages. It deals, for the most part, with reports on patients who have been referred to hospitals because of infections in the respiratory tract or on children seen in clinics and in practice. This report presents another type of approach to the investigation of the paranasal sinuses in children—the consideration of the paranasal sinuses of the average healthy child.

Data on the growth of the sinuses and the variations in their size at different ages from birth to late adolescence have been reported previously.[1] This paper represents an analysis of the evidences of infection of the respiratory tract as obtained from the history, the physical examinations and the roentgenograms of the chest and paranasal sinuses in the same group of average healthy children who furnished the material for the previous study.

### MATERIAL

As was explained in part I of this study,[1] the Child Research Council has been actively engaged in gathering data on average healthy children for many years. Each child is examined at regular intervals from birth to maturity. As part of this study, routine posteroanterior roentgenograms of the chest and paranasal sinuses are taken, the clinical history is recorded and a complete physical examination is done with care each time a child is examined, which is usually four times each year. Since no films were taken of the sinuses of these children before 1925, the series of some of the older children begin as late as three or four years after birth. In all instances, however, the examinations have been continuous to the present age of the child.

Among the 100 children who comprise the material of this study, there are 42 girls and 58 boys. The 3 youngest children have been followed up to 5 years

From the Child Research Council and the University of Colorado School of Medicine.

1. Maresh, M. M.: Paranasal Sinuses from Birth to Late Adolescence: I. Size of the Paranasal Sinuses as Observed in Routine Posteroanterior Roentgenograms, Am. J. Dis. Child. **60**:55 (July) 1940.

of age. The oldest children have been followed up to between 16 and 17 years of age. There has been a total of 3,501 roentgenograms of the sinuses taken of these 100 children and an equal number of films of the chest.

The series of films of 72 of the 100 children begin with roentgenograms taken within the first few months or at least within the first year of life. The present ages of these 72 children range from 5 to 14 years, with the following distribution: 5 years, 3 children; 6 years, 3; 7 years, 25; 8 years, 11; 9 years, 10; 10 years, 6; 11 years, 2; 12 years, 8, and 14 years, 4. The total number of roentgenograms of the sinuses taken of these children during the period between 1 year 1 month of age and the present age is 2,102. The average number of films of the sinuses taken per year for each child is 3.8. Only 6 children have had less than an average of 3.5 films taken per year after the first year. During the first year all but a few children were examined five or six times. Obviously, the number of roentgenograms of each of the 72 children varies, depending on the number of years the child has been followed. The oldest children have had over 50 roentgenograms of the sinuses taken during the period between 1 year of age and the present, while each of the 3 children 5 years old has had 15 or 16 films taken.

In attempting to correlate the results of the roentgenographic examination with those of the rest of the examination, it became necessary to eliminate those examinations in which either the history during the interval since the previous examination or the physical examination was incomplete. Since the sinuses are rarely aerated in the first films after birth, those examinations made before 6 months of age were also omitted. There remained, however, 2,614 complete examinations of the 100 children that were suitable for analysis. The number of examinations of any 1 child ranged from 10 to 39 with only a few children having either less than 20 or more than 30 examinations each.

## METHOD OF STUDY

Certain explanations should be made regarding the interpretation of the roentgenograms and the evaluation of the clinical history and the results of physical examination.

If the films showed obviously decreased translucency of any of the sinuses, the sinus was considered "pathologic," although in each instance notations were made to show whether the sinus was completely radiopaque, whether the mucous membrane of the antrums appeared thickened or whether the sinus was considered dull only as compared with the radiotranslucency of the other sinuses. Since only posteroanterior films were taken routinely, the sphenoid sinuses were not considered in this study. If any of the sinuses observed in the roentgenogram did not have clear sharp borders and were not entirely radiotranslucent, the sinus was classified as "pathologic." This term will be used throughout this paper to denote any roentgenogram in which all the sinuses did not appear normally clear.

If a child had no cold or other infection of the respiratory tract at the time of the examination and had not had such an infection within the preceding two weeks, that examination was classified as "negative" for history of infection of the respiratory tract.

The task of determining what were significant findings in the nose and throat was more difficult. The records of the physical examinations by the staff pediatricians include all the observations on the nose and throat. Mucoid nasal discharge and postnasal discharge, frequently noted in infants who are crying and struggling against the examination, were not considered significant. Slight nasal

TABLE 1.—*Significant Observations in One Child* *

| Age | | Roentgen Examination | | | | | | | Clinical Examination | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ethmoid Sinuses | | Antrums | | Frontal Sinuses | | | | | |
| Yr. | Mo. | Chest | L | R | L | R | L | R | Nose | Throat | Chest | History |
| .. | 6 | — | — | — | — | — | .. | .. | — | — | — | — |
| .. | 9 | — | — | — | + | — | .. | .. | — | — | — | — |
| 1 | .. | — | + | — | + | — | .. | .. | — | — | — | — |
| 1 | 4 | — | — | — | — | — | .. | .. | — | — | — | — |
| 1 | 6 | — | + | — | + | — | .. | .. | — | Generalized redness of throat | Harsh breath sounds | Bronchopneumonia recently |
| 1 | 10 | — | — | — | — | + | .. | .. | — | Slight exudate over tonsils | — | — |
| 2 | 1 | — | + | + | — | — | — | .. | — | Tonsils slightly injected | — | — |
| 2 | 4 | — | — | — | — | — | — | .. | — | — | — | — |
| 2 | 8 | — | — | — | — | — | — | — | — | — | — | — |
| 2 | 10 | — | — | + | + | + | — | — | — | — | — | — |
| 3 | 1 | — | + | + | + | + | — | — | — | — | — | Severe sore throat 10 days before |
| 3 | 3 | — | — | + | — | + | — | — | Moderate crusting | Tonsils and pillars red | — | — |
| 3 | 6 | — | + | + | + | + | + | + | — | — | — | — |
| 3 | 9 | — | + | + | + | + | — | — | — | — | — | — |
| 4 | 1 | — | — | — | — | — | — | — | — | — | — | — |
| 4 | 4 | — | — | — | + | — | — | — | — | — | — | — |
| 4 | 6 | + | — | — | — | + | — | — | Red, congested mucous membrane | Pharynx congested | Coarse rales and rhonchi | Cold with cough and wheezing week before |
| 4 | 9 | — | — | — | — | + | — | — | — | — | — | — |
| 5 | .. | — | + | + | + | + | — | — | — | — | — | — |
| 5 | 3 | — | — | — | — | — | — | — | — | — | — | — |
| 5 | 6 | — | — | — | — | — | — | — | — | — | — | — |
| 5 | 10 | — | — | — | — | + | — | — | — | Tonsillar pillars congested | — | — |
| 6 | .. | — | — | + | — | — | — | — | — | — | — | — |
| 6 | 4 | — | — | — | — | — | — | — | — | — | — | — |
| 6 | 6 | — | — | — | — | — | — | — | Mucous membrane slightly congested | — | — | Cold 10 days before |
| 6 | 9 | — | — | — | — | — | — | — | — | — | — | — |
| 7 | .. | — | — | + | + | — | — | — | Semidried yellow exudate, bilateral | Tonsillar pillars injected | — | — |
| 7 | 3 | — | — | — | + | + | — | — | — | Generalized redness about tonsils and pillars | — | — |
| 7 | 6 | — | — | — | — | — | — | — | — | — | — | — |
| 7 | 9 | — | — | — | — | — | — | — | Mucopurulent discharge | — | — | Mild cold 2 weeks before |
| 8 | .. | — | — | — | + | + | — | — | Dried purulent exudate | Purulent postnasal drip | — | Severe cold recently |
| 8 | 3 | — | — | — | — | + | — | — | — | — | — | — |

* This same method of tabulation of observations was used for each of the 100 children. The plus sign indicates "pathologic" observations in the roentgenogram. The minus sign indicates no significant "pathologic" observations in the roentgenogram, physical examination or interval history.

crusting was not considered significant, since it is almost universally observed in the dry climate of Colorado. The size of the tonsils was not considered significant if there was no injection, exudate or reddening of the tonsillar pillars. The more common significant changes were purulent, mucopurulent or seropurulent nasal or postnasal discharge, edema and increased redness of the mucous membrane of the nose or throat, injection of the tonsillar pillars, tonsils, tonsillar fossae or pharynx, tonsillar exudate and moderate or marked nasal crusting.

To illustrate further this type of tabulation, the significant material from the examinations of 1 child is given in table 1. This material lends itself admirably to both cross sectional and longitudinal analysis. By arranging the data in sections representing different age levels, cross sectional analysis becomes relatively simple. Although the children are of different ages, the distribution is such that there is a sufficient number of roentgenograms for each age up to 12 years to make the calculations significant.

The 72 children for whom there were series of roentgenograms of the sinuses beginning within the first year of life lent themselves, naturally, to study by the longitudinal method. The data on each child were summarized and compared with those of the rest of the group. The roentgenograms of the sinuses of this group were analyzed for total incidence of "pathologic" antrums, the age at which the individual sinuses first appeared normally aerated on the roentgenograms, the coincidence of asymmetric antrums and unilateral involvement of the antrums and the development of the frontal sinuses.

The results of the examinations which were complete and reliable with regard to the history, physical examinations and roentgenograms of the sinuses were analyzed for all possible correlations between the roentgenograms and the clinical evidence of infection of the respiratory tract. An attempt was also made to discover what possible influence such factors as tonsillectomy, allergy or incidence of colds bore on the clinical and roentgenographic evidence of infection of the respiratory tract.

The films of the chest were more difficult to classify, since the normal variations in hilar structures and pulmonary markings are so extreme. We have regarded as a whole the series of films for each child and have attempted to show these variations.

## RESULTS

The chief problem in a survey of this nature is not so much in the actual work itself as in trying to show what the results have been. In an attempt to simplify the description of the results, those calculations which were not especially significant are either described briefly or not mentioned at all. Much of the work could not be illustrated either by tables or by charts because of the nature of the data.

*Cross Sectional Analysis of 3,501 Roentgenograms of the Sinuses of 100 Children for "Pathologic" Antrums.*—Table 2 gives the results of the analysis of all but 240 of the 3,501 roentgenograms of the sinuses of the 100 children for incidence of "pathologic" antrums. The number of children between the ages of 12 and 17 years was less than 30, and the number of films for each yearly age group between those ages was less than 100. Therefore, calculations are probably not significant and are not included in this table. The table, made up of data from the roentgenograms of children who have been followed for varying numbers of

years, does not, of course, include material from the analyses of films of all 100 children at every given age. Figure 1 illustrates graphically the percentages given in table 2, of antrums which were not normally clear.

The high percentage of films taken between birth and the age of 1 year in which the antrums were not clear is due to the fact that the sinuses do not usually appear clear in roentgenograms until about the age of 6 months. Since this slow postnatal aeration of the sinuses is probably a physiologic rather than a pathologic process, some of the significance of the high percentage of "pathologic" antrums in the first year of life may be discounted.

TABLE 2.—*Analysis of the Roentgenograms of the Sinuses of One Hundred Children*

| Age Interval | Birth to 1 yr. | 1 yr., 1 mo. to 2 yr. | 2 yr., 1 mo. to 3 yr. | 3 yr., 1 mo. to 4 yr. | 4 yr., 1 mo. to 5 yr. | 5 yr., 1 mo. to 6 yr. | 6 yr., 1 mo. to 7 yr. | 7 yr., 1 mo. to 8 yr. | 8 yr., 1 mo. to 9 yr. | 9 yr., 1 mo. to 10 yr. | 10 yr., 1 mo. to 11 yr. | 11 yr., 1 mo. to 12 yr. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of children | 77 | 85 | 90 | 98 | 100 | 99 | 96 | 83 | 62 | 49 | 45 | 35 |
| Total number of films examined | 376 | 291 | 315 | 356 | 353 | 345 | 332 | 270 | 203 | 170 | 141 | 109 |
| Total number of films with 1 or both antrums not normally clear | 219 | 93 | 112 | 121 | 117 | 117 | 98 | 78 | 54 | 29 | 27 | 15 |
| Percentage of films in which 1 or both antrums were not normally clear* | 58.2 | 32.0 | 35.5 | 34.0 | 33.1 | 33.9 | 29.5 | 28.9 | 26.6 | 17.1 | 19.1 | 13.8 |
| Number of children with normally clear antrums in every film taken during a given year | 4 | 34 | 28 | 31 | 37 | 32 | 45 | 44 | 34 | 32 | 29 | 29 |
| Percentage of children with normally clear antrums in every film taken during a given year† | 5.2 | 40.0 | 31.1 | 31.6 | 37.0 | 32.3 | 46.9 | 53.0 | 54.8 | 65.3 | 64.4 | 82.8 |

* These percentages are illustrated graphically in figure 1.
† These percentages are illustrated graphically in figure 2.

It will be noted in both table 2 and figure 1 that there is a relatively constant percentage of "pathologic" antrums in the films taken between 1 year and 6 years of age, the range being between 32 and 35.5 per cent. From 6 to 12 years of age this percentage drops steadily to approximately 15 per cent. This incidence of "pathologic" antrums is further borne out by listing the percentage of the total number of children who had normally clear antrums in every film taken during any given age period. These figures, given in table 2 are also illustrated in figure 2.

Figure 2 is nearly a reversal of figure 1 as would be expected if it is assumed that the "pathologic" antrums are not equally divided among all the children every year. For instance, there are 98 films showing such antrums of a total of 332 films of 96 children taken between the ages of 6 and 7 years. If these were distributed equally among all the

children, each child would have had at least 1 film with "pathologic" antrums. But actually (as shown in fig. 2) at this age level 45 of the 96 children had nothing but clear sinuses in their roentgenograms. Moreover, we have observed rather frequently that a given child shows diminution in the number of films demonstrating "pathologic" antrums after 6 or 7 years of age and, in many instances, will show normally clear sinuses in nearly all films taken thereafter. Figure 2 shows this increase in the

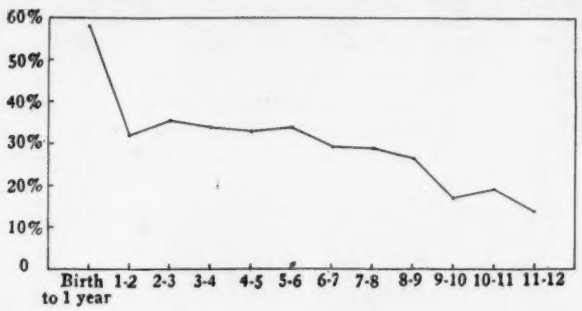


Fig. 1.—Graph showing percentage of the total number of roentgenograms of children in each age group in which one or both antrums were not clear. The age groups in this illustration and in figure 2 range from birth to 1 year; 1 year 1 month to 2 years, 2 years 1 month to 3 years, etc., up to the age of 12 years.

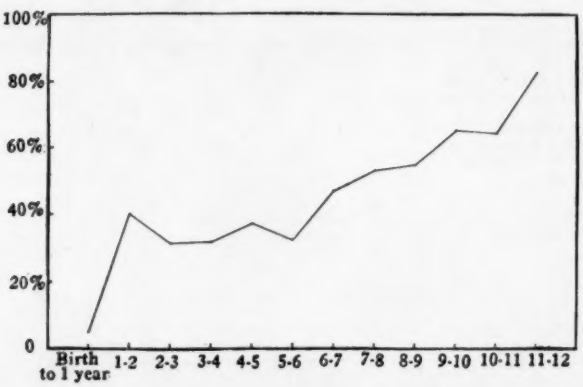


Fig. 2.—Graph showing percentages of the total number of children in each age group whose antrums were normally clear in every roentgenogram taken during the year.

percentage of children with clear sinuses in the yearly intervals after 6 years of age. In general, the figures for the intervals from 12 to 17 years of age follow the pattern of those for the tenth, eleventh and twelfth years. It must not be assumed, however, that these routine roentgenograms are always clear after the age of 12 years.

*Longitudinal Analysis of 2,102 Roentgenograms of the Sinuses of 72 Children Who Have Been Followed from the First Year of Life to the Present.*—The longitudinal analysis of the films of the 72 children who have been followed from within the first year of life to their present age yielded a great deal of information. No films taken before the age of 1 year were included in this part of the analysis, in order to eliminate the question of whether the antrums were actually "pathologic" or whether there was merely a delaying of the normal physiologic process of postnatal aeration of the sinuses.

Twelve children in this group of 72 showed "pathologic" antrums (one or both) in less than 12 per cent of the total number of films taken between the age of 1 year and 1 month and the present age; 24 children showed such antrums in only 13 to 25 per cent of the total number of films; 16 children were in the group showing 26 to 37 per cent; 7 were in the 38 to 50 per cent group; 8 in the 51 to 62 per cent group; 2 in the 63 to 75 per cent group and 3 in the 76 to 87 per cent group. The mean percentage of films showing "pathologic" antrums for all 72 children was 30.7 per cent.

Some children showed normally aerated sinuses sooner after birth than others. Two children showed normally clear antrums and ethmoid sinuses in the first films taken at 1 month of age. Five more children showed clear sinuses at 2 months of age. By 7 months of age 54 per cent (39 children) and by 1 year of age 71 per cent (51 children) had clear sinuses. Four children did not show all sinuses normally clear till after 2½ years of age. Since these figures are based on the time when both ethmoid sinuses and both antrums were clear in the same film, they probably do not represent the physiologic process of aeration of the sinuses. In some instances, for example, one antrum remained cloudy for months or even years after the other antrum had cleared normally within a few months of birth. Thus the delayed aeration of one antrum may often have represented a pathologic process. Other children showed one antrum clear in an early film, that antrum "pathologic" and the other antrum or the ethmoid sinuses clear in the next film but not all sinuses clear at the same time during the first year. Mean values for the time when each sinus first appeared clear in the roentgenograms are probably not significant, but as calculated for this group of 72 children they were 5½ months for both right and left ethmoid sinuses, 7½ months for the left antrum and 9 months for the right antrum.

These observations led us to consider whether the age at which the sinuses first appeared clear in the roentgenograms bore any relation to the appearance of the sinuses after the first year of life, that is, whether the children whose antrums were aerated early showed clearer sinuses thereafter than did those whose sinuses were slower to become normally clear. The attempt to determine this relation necessitated arbitrarily

setting an age by which time the sinuses should be clear. The antrums (not both antrums and ethmoid sinuses) were both normally clear by 7 months of age in 43 of the 72 children (60 per cent). This group of 43 children we called, arbitrarily, the "early group." The mean percentage of "pathologic" antrums for the 72 children, given before, was 30.7 per cent, while the 43 children in the "early group" had an average of 26.1 per cent. The 29 children whose antrums were not normally clear by 7 months of age we called the "slow group." They showed a significantly higher average percentage of "pathologic" antrums, namely, 38.2 per cent. Although there were only 29 in the "early group" of 43 children who had individual percentages of "pathologic" antrums that were below the mean for the whole group of 30.7 per cent, as compared with 12 children in the "slow group" of 29, statistical calculation of $\chi^2$ shows that there is a significant relation between the time of postnatal aeration of the antrums and the percentage of "pathologic" antrums in films taken after 1 year of age.

*Relation Between Size and Asymmetry of the Sinuses and Frequency of Infection, as Visualized in Roentgenograms of the Sinuses.*—So far only the number of films that showed "pathologic" antrums has been considered, without regard to whether the changes were bilateral or predominantly one sided. In a group of 64 children who have been followed from within the first year of life to the age of 7 years, the distribution of total "pathologic" antrums in the films taken between the ages of 1 and 7 was much like that of the previous groups mentioned, ranging from 0 to 95 per cent of all the films taken during those years, with a mean of 35 per cent. Separating from this total number of films showing "pathologic" antrums, however, those films which showed only unilateral changes demonstrates that in the usual instance both antrums are more frequently involved than one alone. The range of percentages of total number of films showing only changes in the left antrum is from 0 to 38 per cent, with 27 of the 64 children having no films with any such changes. The percentages of total number of films showing only changes in the right antrum range from 0 to 86 per cent, but 20 of the 64 children had no films taken during this age period which show only right-sided involvement. This difference between the total percentage of roentgenograms showing "pathologic" antrums and the percentage showing only unilateral changes is presented in table 3. Even though the usual child is more apt to have bilateral "pathologic" antrums, every abnormal film of a few children showed changes in only one antrum.

As stated before, in part I of this study,[1] the antrums sometimes appear asymmetric as regards both size and shape, but the difference in size between the two antrums was usually not marked. The antrums were considered of equal size if the two sets of measurements were within

2 mm. of each other. Of the 64 children who have been followed from the first year of life to the age of 7, only 8 showed differences in size of the antrums that were readily apparent on measuring the diameter of the two antrums. It has been frequently stated in the literature that infection within a sinus during infancy will inhibit the growth of that sinus and will affect the development of the frontal sinus. Detailed analysis of the films of the 8 children with definitely asymmetric antrums brought out some interesting information. Seven of the 8 children had more than the mean percentage of films showing "pathologic" antrums. However, the 1 child who had less than the mean percentage had antrums that were of approximately equal size till the age of 4½ years and has never shown a preponderance of either right-sided or left-sided antral changes. He is now 11 years old; the antrums are definitely

TABLE 3.—*Distribution of Sixty-Four Children According to the Percentage of Roentgenograms Taken Between One and Seven Years of Age Which Show "Pathologic" Antrums*

| Percentage* of the roentgenograms of each child taken between 1 and 7 years of age which show "pathologic" antrums | % 0 | % 1-12 | % 13-25 | % 26-37 | % 38-50 | % 51-62 | % 73-75 | Over 75% |
|---|---|---|---|---|---|---|---|---|
| Number of children with either or both antrums "pathologic" from 1 to 7 years | 1 | 7 | 19 | 13 | 12 | 5 | 2 | 5 |
| Number of children with only bilaterally "pathologic" antrums from 1 to 7 years | 5 | 23 | 18 | 11 | 4 | 3 | 0 | 0 |
| Number of children with only left antrum "pathologic" from 1 to 7 years | 27 | 27 | 7 | 2 | 1 | 0 | 0 | 0 |
| Number of children with only right antrum "pathologic" from 1 to 7 years | 20 | 32 | 7 | 2 | 1 | 1 | 0 | 1 |

* Figured for each child thus:

$$\frac{\text{Roentgenograms showing "pathologic" antrums taken between 1 and 7 years of age}}{\text{Total roentgenograms of the sinuses taken between 1 and 7 years of age}}$$

asymmetric, and his series of films of the sinuses has consistently shown a percentage of "pathologic" antrums below the mean. Another child has had asymmetric antrums since the first year of life and has had only bilateral involvement of the antrums in the films of his sinuses since birth. Four of the other children with asymmetric antrums are in the upper 10 per cent of those with unilateral antral changes up to 7 years of age. In each child the smaller antrum is the one that has been frequently "pathologic," while the opposite antrum has been cloudy only when both were involved. In each instance, however, the asymmetry was evident soon after birth, and one might as well say that the asymmetry was responsible for the unilateral antral changes as to say that the infection was responsible for the asymmetry. The other 2 children were also in the upper 10 per cent of the children with unilateral "pathologic" changes up to 7 years of age but they show the opposite picture, that is, the larger of the two asymmetric antrums was the one showing the frequent "pathologic" changes.

The child who has had the most marked unilateral "pathologic" changes of all the children has had antrums of equal size throughout and is now 12 years old, although 19 of his 22 films taken between 1 and 7 years of age show only right-sided antral changes. And another child whose every abnormal film among those taken between 1 and 7 years of age shows only the right antrum to be involved also has antrums of equal size at his present age of 9 years.

We were also interested in determining whether the amount or type of antral involvement between 1 and 7 years had any influence on the development of the frontal sinuses. Since the time of appearance of the frontal sinuses varies greatly, it seemed logical that infections during this age period might be of some importance in influencing the development of these sinuses. We were, however, unable to find any correlation between either the number or the type of "pathologic" antrums and the development of the frontal sinuses.

Two of the 8 children with asymmetric antrums had both frontal sinuses well developed by the age of 7 years, and in each the larger frontal sinus was on the same side as the smaller antrum. One child had a well developed frontal sinus on the side of the smaller antrum and little development of the frontal sinus on the other side. All of the other 5 children with asymmetric antrums were in the group with poorly developed frontal sinuses; in 3 children the developing frontal sinuses were of equal size.

When the children with symmetric antrums were considered, the development of the frontal sinus bore some questionable relation to the frequency with which the antrums appeared to be "pathologic." The children with either or both frontal sinuses well developed somewhat more frequently had a total percentage of "pathologic" antrums below the mean for the group. However, this was not true in one third of the children and is inconclusive. And in 11 children in whom the total percentage of "pathologic" antrums was less than 20, only 4 had either or both frontal sinuses developed above the level of the orbital roofs, while the other 7 had poorly developed frontal sinuses. There seems to be, therefore, no pattern of growth of the frontal sinuses that can be interpreted as being related consistently to the number of "pathologic" antrums or to the type of antral changes in the children whom we have studied.

The next question was whether there is any relation, after the first year, between the size of the antrums and the number of films showing "pathologic" changes. The range in size for antrums at each age level was given in part I of this study. With elimination of the 8 children with asymmetric antrums there remained 56 who were divided into four groups according to the size of the antrums. If infection inhibits the growth of the antrums, one would expect to find the largest antrums

in those children with the least evidence of infection. We found, however, that only one third of the children with large antrums (fourth group) were among those with less than 20 per cent of "pathologic" antrums in films taken between 1 and 7 years of age, while the majority of the rest were above the mean. Likewise, only about one half of the children with small antrums (first group) were above the mean for percentage of "pathologic" antrums in films taken between 1 and 7 years.

*Cross-Sectional Analysis of 2,614 Examinations of 100 Children, Correlating the Evidence Obtained from the History, the Physical Examination and Roentgenograms of the Sinuses.*—Since the 2,614 complete examinations of these 100 children showed an appreciable increase in the number of clear sinuses and completely negative results after 6 years of age, the data were also arranged for the two approximately equal groups—those examinations performed between the ages of 6 months and 5 years 11½ months and those made between the age of 6 years and the present age of each child. Figure 3 shows the result of this tabulation in graphic form.

It will be observed that 40 per cent of the results of 2,614 examinations were negative; that is, no history of infection of the respiratory tract was elicited, sinuses were clear in the roentgenograms and there were no significant findings in the nose or throat. Forty and two-tenths per cent of the examinations showed significant clinical changes in the nose or throat. Thirty-four and three-tenths per cent of the total number of examinations showed one or more "pathologic" sinuses in the roentgenograms. Twenty-eight and six-tenths per cent of the examinations were made coincident with or within two weeks of a recent infection of the respiratory tract.

It was interesting to note that of the reports on 40.2 per cent of examinations revealing significant changes in the nose or throat, only slightly more than a third also included both a recent history of infection of the respiratory tract and one or more "pathologic" sinuses shown in the roentgenograms. Likewise, of this same group shown with positive clinical findings in the nose or throat, only half had a recent history of infection of the respiratory tract and less than half showed one or more "pathologic" sinuses.

Of the 34.3 per cent of the examinations revealing "pathologic" sinuses in the roentgenograms, slightly less than half were in cases with a history of recent infection of the respiratory tract.

Of the 28.6 per cent of examinations made either at the time of or within two weeks of a cold or other infection of the respiratory tract, slightly less than half showed normally clear sinuses. For this group, however, the examinations between 6 months and 5 years 11½ months of age showed a smaller proportion of clear sinuses than those performed after 6 years of age.

Since these figures are based on the observations at routine examinations of average children, it does not seem safe to predict from any one observation what the rest of the examination will show.

It seemed wise to attempt to discover if the frequency of colds (including those which did not occur at the time of the examinations),

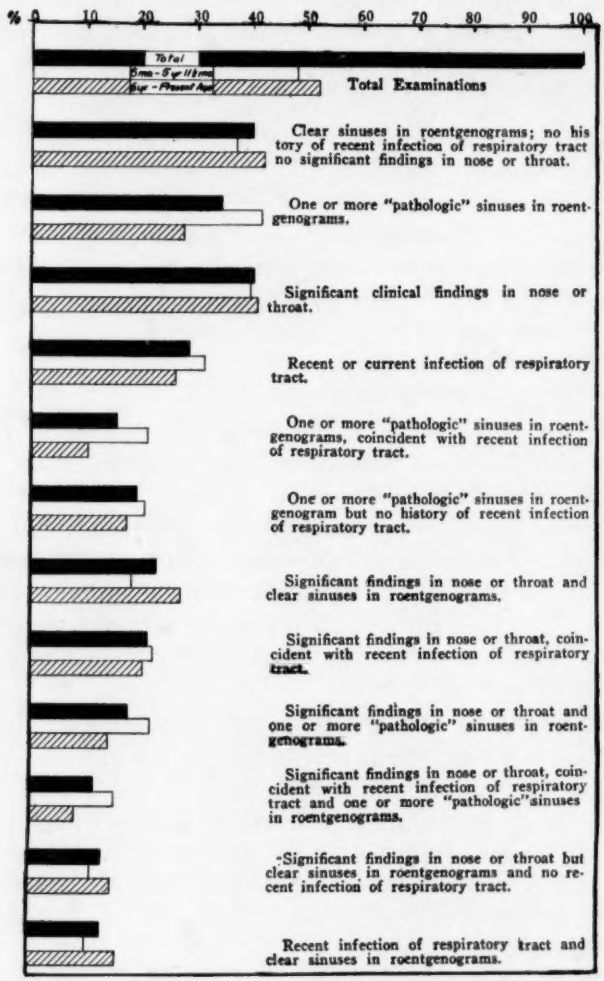
%
0
10
20
30
40
50
60
70
80
90
100
Total
6 mo. - 5 yr. 11½ mo.
6 yr. - Present Age
Total Examinations
Clear sinuses in roentgenograms; no history of recent infection of respiratory tract no significant findings in nose or throat.
One or more "pathologic" sinuses in roentgenograms.
Significant clinical findings in nose or throat.
Recent or current infection of respiratory tract.
One or more "pathologic" sinuses in roentgenograms, coincident with recent infection of respiratory tract.
One or more "pathologic" sinuses in roentgenogram but no history of recent infection of respiratory tract.
Significant findings in nose or throat and clear sinuses in roentgenograms.
Significant findings in nose or throat, coincident with recent infection of respiratory tract.
Significant findings in nose or throat and one or more "pathologic" sinuses in roentgenograms.
Significant findings in nose or throat, coincident with recent infection of respiratory tract and one or more "pathologic" sinuses in roentgenograms.
Significant findings in nose or throat but clear sinuses in roentgenograms and no recent infection of respiratory tract.
Recent infection of respiratory tract and clear sinuses in roentgenograms.

Fig. 3.—Incidence of examinations revealing significant findings in the nose or throat, a recent history of infection of the respiratory tract and appearance of one or more "pathologic" sinuses in the roentgenograms and combinations of these findings in 2,614 complete examinations of 100 children. The solid black graphs indicate percentage of the total number of examinations. The white graphs indicate percentage of the total number of examinations performed between 6 months and 5 years, 11½ months of age. The cross-hatched graphs indicate percentage of the total number of examinations performed between 6 years of age and the present.

the presence of allergic manifestations or tonsillectomy bore any relation to the results of the physical and roentgen examinations of the children. The data are not important enough to be presented in tabular form, but there were a few interesting observations. The mean number of colds in the first six years of life for 83 children for whom the interval records were complete during this age period was slightly over 11. The group with less than the mean number of colds showed a slightly higher percentage (63 per cent) of clear films of the sinuses between 6 months and 6 years of age than the group with more than the mean number of colds (52 per cent).

The children with definite allergic manifestations showed a higher percentage of films with "pathologic" sinuses (49 per cent) up to 6 years of age than did the group with no evidence or doubtful evidence of allergy (38 per cent). After 6 years of age there was no essential difference between the data of the allergic and the nonallergic groups. It was interesting to note, in this connection, that 26 of the 100 children had shown repeated and definite evidences of allergy. There are about 8 more children in whom allergy is suspected, but they were classified with the nonallergic group.

Tonsillectomy apparently had no influence on the incidence of "pathologic" sinuses. The children with tonsillectomy before 6 years of age did show, however, a slight decrease in the incidence of signicant changes in the nose and throat or history of infection of the respiratory tract after 6 years of age.

There were several other observations that seem worthy of brief comment. It seems striking that tenderness of the sinuses was never noted in any of the children. Only 1 child complained of headaches at the times when the sinuses were found to be "pathologic" in the roentgenogram. Only 60 per cent of the examinations showing purulent nasal discharge also revealed "pathologic" sinuses in the roentgenogram, and about three fourths of these "pathologic" sinuses were in roentgenograms taken before 6 years of age. Of the 40 per cent of examinations which showed purulent nasal discharge and clear sinuses, two thirds were performed after the age of 6 years.

The question of whether these children received any treatment for infections of the sinuses will undoubtedly arise. No treatments are ever given by the staff of the Child Research Council. Of course, some of the children are seen by the family pediatrician or otolaryngologist, either before or after their examinations by the staff of the Child Research Council, if their condition warrants such a procedure. There is not a complete check on what type of treatment was given or how intensive such treatment has been. It is, however, fairly safe to say that by far the greatest number of children in this group with minor infections of the respiratory tract are not treated except by simple home remedies.

We know definitely of a few children who have had fairly intensive treatment for infection of the sinuses. They do not appear to have made any more rapid recovery than those whose infections were untreated. Our observations on these children over a period of years suggest that children with these roentgenographic findings are too frequently over-treated and that the average child will usually have clear sinuses within a short time if untreated. Perhaps it is not even justifiable to call the condition represented by these changes in the roentgenograms of the

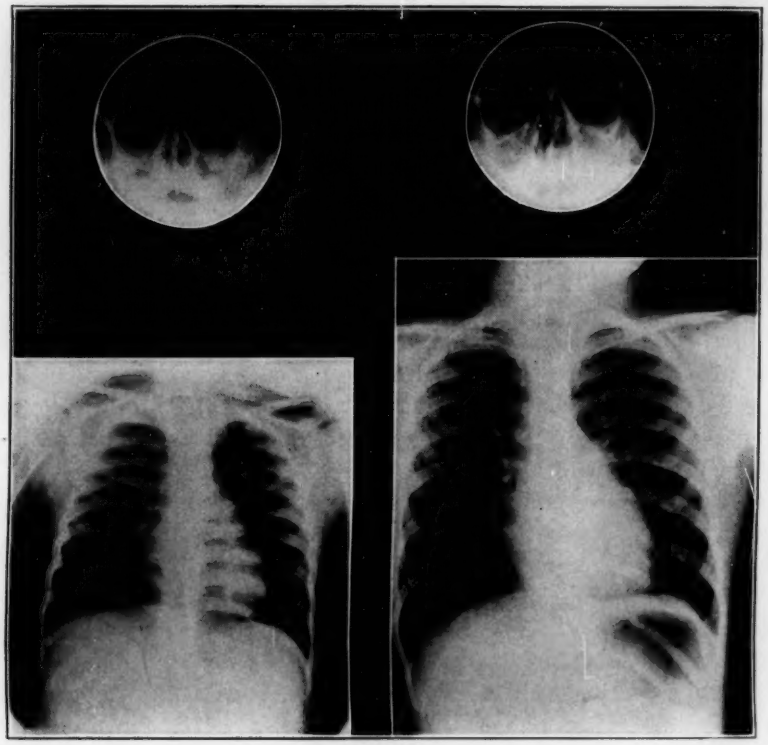

Fig. 4.—Figures 4 to 6 are roentgenograms taken early (those on left side) and recently (those on right side) of 3 children with far more than the usual number of pathologic sinuses on their roentgenograms. The photographs show the wide variation in size and density of hilar structures and pulmonary markings. In each instance structures seen in the recent roentgenogram of the chest can be identified in the earlier film. This illustration (fig. 4) shows films of the first subject, taken at 2 years and 8 years of age, respectively.

sinuses of children a true "sinusitis." Certainly the vast majority of the children do not appear to be ill or even below par when the sinuses are not clear in the roentgenograms. It has been a continual shock to us for several years to observe the frequency with which completely

opaque sinuses are seen in the roentgenograms in the absence of clinical signs of infection. Since the children seen by the staff of the Child Research Council are average healthy children, it seems justifiable to say that the roentgenographic evidence usually accepted as indicative of infection of the sinuses is to be found much more frequently than is commonly supposed.

*Variations in the Roentgenograms of the Chest.*—The problem of what constitutes the "normal" hilus and the "normal" perivascular and

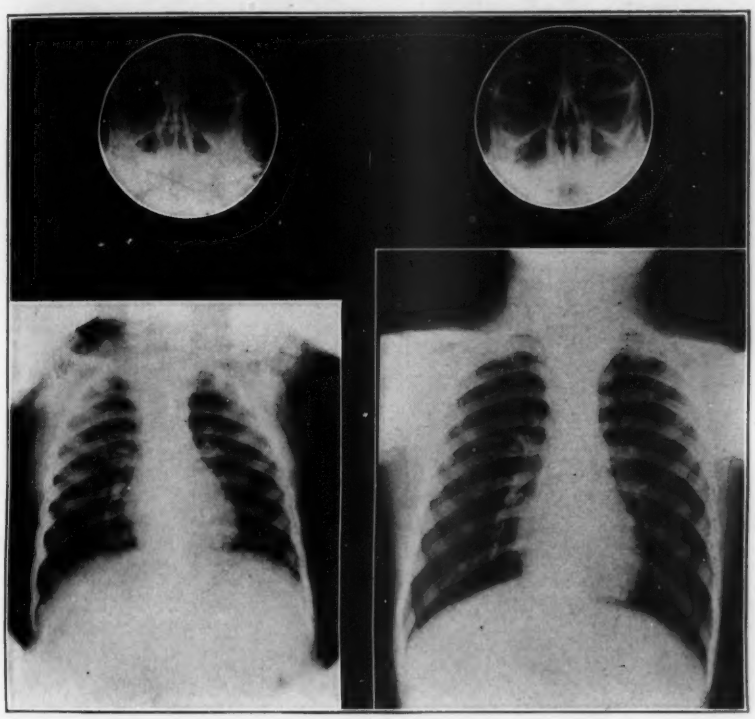

Fig. 5.—Films of the second subject, taken at 2 years and 7 years of age, respectively.

peribronchial markings in childhood has long concerned the roentgenologist and the pediatrician. The tendency of many workers in this field has been to interpret the films of the chest in the light of the history of infections of the respiratory tract and to relate infections of the sinus to infections of the chest, calling attention to the increased width of the hilar shadow and accentuations of peribronchial and perivascular markings as evidences of nontuberculous disease of the chest. This concept has been generally accepted and has also been reported in the past as the point of view of some members of the staff of the Child Research

Council.[2] However, during the last decade, with long term follow-up examinations of this group of healthy children, we have come to feel that these variations in appearance of the hili and markings of the lung are as much a part of the individual variations observed in growth and development as the variations in size and shape of the cardiac silhouette, in the time of ossification of the epiphysial centers or in external measurements and proportions of the body. We have observed that the

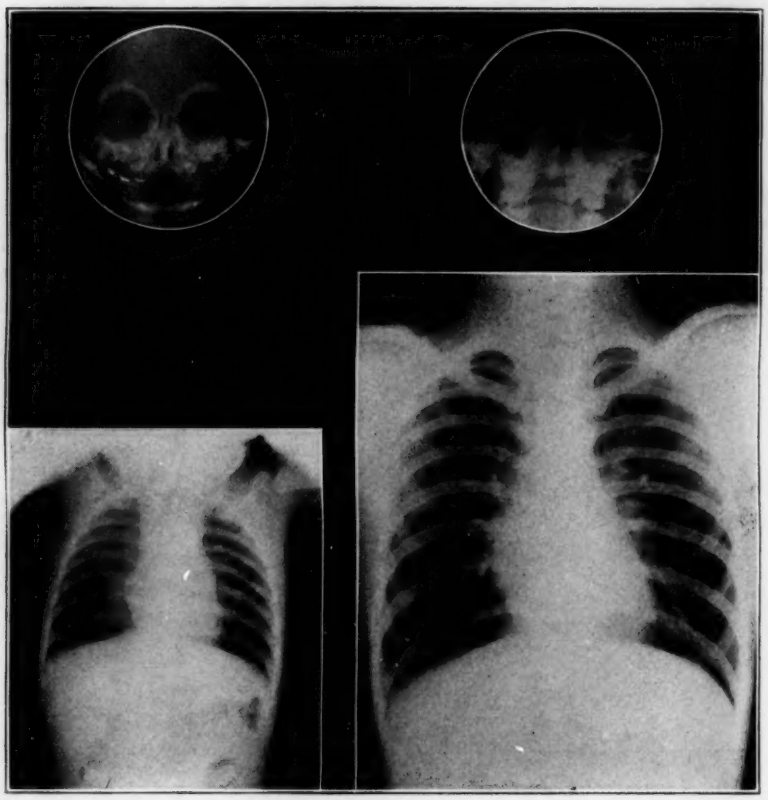

Fig. 6.—Films of the third subject, taken at 6 months and 10 years 6 months of age, respectively.

roentgenograms of this group of healthy children show no essential changes, except those due to growth, in the appearance of the chest from the first year of life throughout the rest of the series—that is to say, each child establishes his own "normal" for appearance of the hilar shadows and pulmonary markings soon after birth. Although it may

2. Wasson, W. W., and Waltz, H. D.: Relationship of Sinus Disease to Chest Disease in Children, Radiology **22**:432 (April) 1934.

be profitable to compare a child's films with those of other children, he should not be judged by what is characteristic or "normal" for another child. This constancy of appearance is, of course, best illustrated by observing all the films of each child at one time. As an illustration, we have reproduced in figures 4 to 9 roentgenograms of the chest of 6 children; an early film and one taken during the last few months are shown for each child. Careful study of each such pair of roentgenograms will show that the same hilar shadows and the same pulmonary

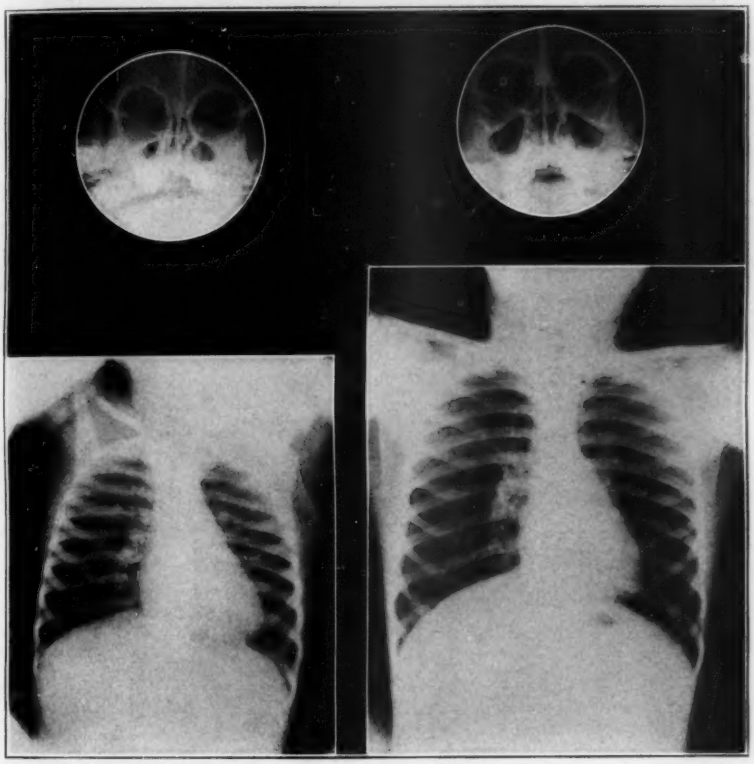

Fig. 7.—Figures 7 to 9 are roentgenograms taken early (those on left side) and recently (those on right side) of 3 children whose roentgenograms showed unusually clear sinuses. The roentgenograms of the chest show the same wide range of variation in size and density of hilar structures and in pulmonary markings as those in figures 4, 5 and 6. In each instance the structures seen in the recent roentgenogram can be identified in the early film. This illustration shows films of the first subject, taken at 2 years and 7 years of age, respectively.

markings are present in the early film as in the later one. The roentgenograms of the 3 children in figures 4, 5 and 6 have been selected as representative of the films of all those children who show the greatest total percentages of "pathologic" sinuses on films taken between 1 year

of age and the present time. Light, average and heavy hilar shadows and pulmonary markings all occur in this group of children whose sinuses show considerably more than the average amount of infection, if we accept the roentgenographic changes as evidence of infection of the sinuses. The child whose films are shown in figure 4 had normally clear sinuses in only 6 of the 28 films taken between 1 year of age and the present time. One or both of her antrums were cloudy on the 22

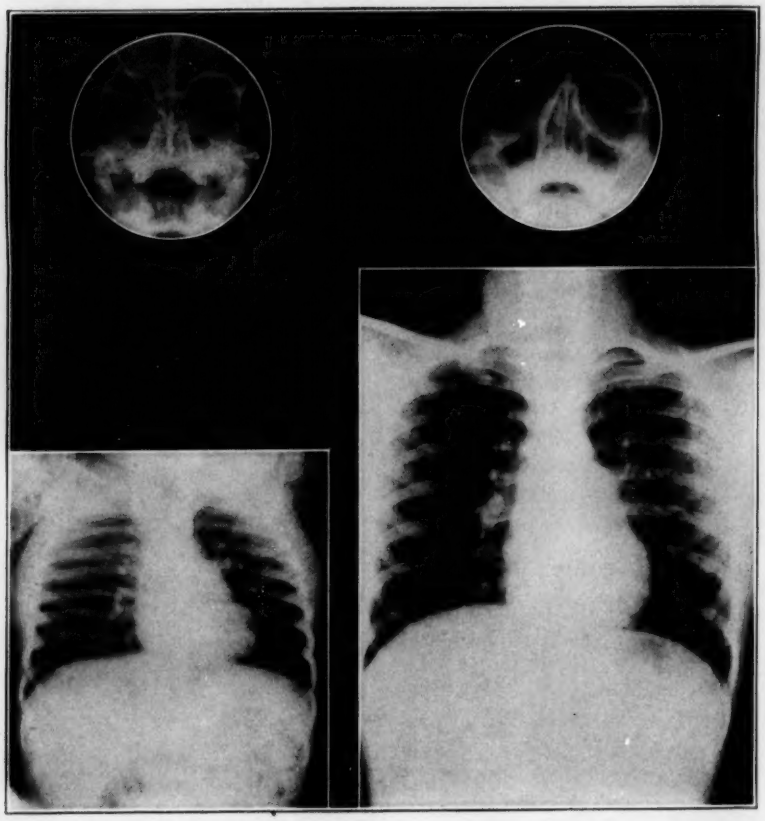

Fig. 8.—Films of the second subject, taken at 2 years and 12 years of age, respectively.

other roentgenograms, yet the series of films of the chest is probably the "clearest" of any of the group: The hili are small and discrete, perivascular and peribronchial markings are inconspicuous and the detail of the lungs is sharp. Figure 6 represents the opposite extreme, in a boy whose films show numerous heavy markings extending from the hili into the middle zones of the lungs. He, too, had a great deal of antral infection, as judged by the roentgenograms. But since all the structures

identified in the last film can also be seen in the early film taken at 6 months of age, we feel that the films of his chest are as "normal" for him as those of figure 4 are "normal" for that child.

In figures 7, 8 and 9 are three other illustrations of these same variations in appearance of the chest, but they are selected from the group of children with definitely less than the average percentage of "pathologic" sinuses. Figure 7, representing the "clearest" of the series of films of the chest, depicts early and later films of a child who had

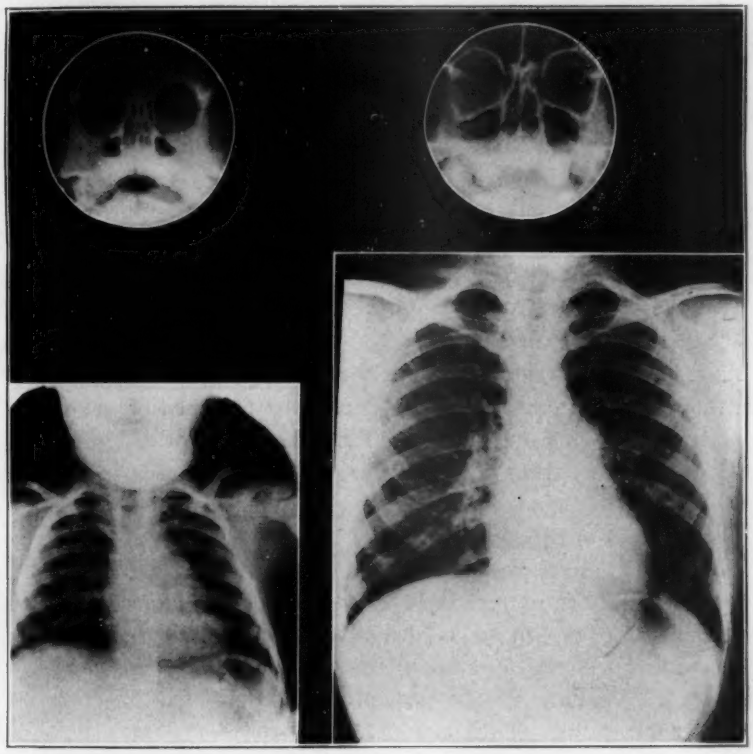

Fig. 9.—Films of the third subject, taken at 1 year 6 months and 11 years 9 months of age, respectively.

normally clear sinuses in 19 of the 24 roentgenograms taken between 1 year of age and the present. Another child, whose films (fig. 9) show broad hili and heavy peribronchial and perivascular markings, had normally clear sinuses in 41 of 43 roentgenograms taken between 1 year of age and the present time.

It must be remembered that the reproductions in figures 4 to 9 are not isolated examples but are truly representative of all the series in this group of 100 healthy children. An occasional child will show some definite pathologic process in the lung during an acute infection or an

allergic attack. However, these do not appear to have any permanent effect on the appearance of the chest. We have seen no evidence of any consistent relation between the roentgenographic evidence of infection of the sinus and the appearance of the chest in these healthy children.

## SUMMARY AND CONCLUSIONS

Our material consists of data collected on average, healthy children who have had roentgenograms taken at regular intervals, without regard to symptoms or signs of disease of the sinuses. We have found in the films all the variations usually attributed to infection without being able to prove any consistent or definite relation between the pattern of development of the sinuses and the incidence of infections.

The cross sectional analysis of the 3,501 roentgenograms of the sinuses of the 100 children who make up this study demonstrated that a relatively constant percentage of the films taken between 1 year and 6 years of age show "pathologic" antrums, that is, between 32 and 35.5 per cent of all films examined. After the age of 6 years, the incidence of "pathologic" antrums drops steadily until it is about 15 per cent at the age of 12.

Analysis of the series of films of the sinuses of 72 children who have been followed from the first year of life to the present time showed that the mean percentage for the group of films showing "pathologic" antrums is 30.7 of all films studied. However, 13 children, or nearly one fifth of the group, have shown "pathologic" antrums in over half their total number of films of the sinuses.

We could find no consistent causal relation between the occurrence of asymmetric antrums and the roentgenographic evidence of infection of the sinuses. Although we could show no correlation between the size of the antrums or of the developing frontal sinuses and the incidence of "pathologic" antrums, we do not mean to imply that infection never influences the growth of the sinuses. The study of an occasional child would lead one to believe that this may be true. What we do wish to emphasize after studying the routine films of these average children is that these variations in size of the sinuses occur frequently, without any demonstrable relation to the amount or frequency of infections as seen in the roentgenogram and without following any definite pattern.

The continuous or longitudinal method of studying individual children makes one cautious about drawing too many conclusions. For instance, we have observed children who have had one antrum that appeared to be definitely infected in every film for several years but whose later films showed normally clear antrums over a period of years. At this time, we do not know of any method of predicting end results on the basis of changes in the sinuses in infancy and early childhood.

The analysis of the roentgenograms of the sinuses, history and results of examinations of the nose and throat showed that 40.0 per cent of the 2,614 examinations of the 100 children gave negative results. Forty and two-tenths per cent of the examinations disclosed significant clinical findings in the nose or throat, but in less than half of these was there roentgenographic evidence of concurrent involvement of the sinuses. Thirty-four and three-tenths per cent of the total number of examinations revealed one or more "pathologic" sinuses in the roentgenograms. Twenty-eight and six-tenths per cent of the examinations were made coincident with or within two weeks of a recent infection of the respiratory tract, and of these less than half showed clear sinuses.

Tonsillectomy had no demonstrable effect on the roentgenographic appearance of the sinuses. The children with less than the mean number of colds in the first 6 years of life showed a higher percentage of normally clear sinuses than did those with more than the mean number of colds for this age period. The children with definitely allergic manifestations (26 per cent of the 100 children) showed a higher percentage of "pathologic" sinuses up to 6 years of age than did the nonallergic group, but after that age there was no essential difference between the data of these two groups.

The appearance of the series of films of the chest of each child leads us to believe that the relation of infection of the sinuses to possible disease of the chest has been erroneously overemphasized in the literature. We found no changes, other than those due to growth, in the hilar shadows and perivascular and peribronchial markings in the films of any child from the age of 1 year to his present age.

The range of "normal" for the roentgenographic appearance of the chest is probably much wider than one has been led to expect. Differences in the films of the chest of the different children demonstrate that the appearance of a child's chest in the roentgenogram is established during the first few months of life and bears no consistent relation to the amount of infection of the sinuses. The "normal" or optimum appearance for one child is not necessarily the same as that for another child.

From the results of this study and those previously reported,[1] it would seem probable that the size and pattern of growth of a child's sinuses and the appearance of the hilar shadows and pulmonary markings in the roentgenogram of his chest are just as much inherent individual characteristics as are the shape of his nose or the color of his eyes.

# INTRACUTANEOUS TESTS WITH PERTUSSIS "TOXIN" AND COMPLEMENT FIXATION TESTS IN WHOOPING COUGH

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In the course of previously reported [1] studies on the therapeutic effect of "detoxified pertussis antigen" the value of a cutaneous test with pertussis "toxin" as an indicator of susceptibility to the disease was studied. At the same time the relation of the complement fixation test for pertussis to cutaneous sensitivity was examined.

Numerous investigators have attempted to demonstrate the reliability of an intracutaneous test, using either pertussis vaccines or extracts of Haemophilus pertussis. There have been conflicting reports in the literature in regard to cutaneous reactions with pertussis toxin. Some authors state that there is a definite relation between the results of cutaneous tests and immunity.[2] Others [3] obtained no correlation between intracutaneous reactions and state of immunity to H. pertussis. Toomey and his associates [4] always found a local reaction after six hours in 680 persons tested with a pertussis filtrate grown on a specially prepared medium. In 502 of the persons tested the local reaction persisted

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From the Willard Parker Hospital and the Pediatric Division of the Bronx Hospital.

1. Lapin, J. H.; Cohen, P., and Weichsel, M.: Arch. Pediat. **56**:590, 1939.

2. Siebler, S. K., and Okrent, S.: J. Pediat. **4**:188, 1934. Thompson, A. R.: J. Hyg. **38**:104, 1938. O'Brien, B.: Lancet **1**:131, 1937. Paterson, D.; Bailey, R. H., and Waller, R. G.: ibid. **2**:361, 1935.

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4. Toomey, J. A., and McClelland, J. E.: Proc. Soc. Exper. Biol. & Med. **31**:34, 1933. Toomey, J. A.; McClelland, J. E., and Lieder, L. E.: ibid. **31**:403, 1933.

for twenty-four hours. In children with whooping cough the reaction was increased when the patients were retested after six to twelve days. That addition of pertussis convalescent serum in different dilutions to pertussis toxin failed to neutralize the toxin was shown by intracutaneous injection into human beings.

The significance of the complement fixation test during active whooping cough and after the injection of various pertussis vaccines has been reported previously.[5] The present paper reports a continuation of these studies. The technic employed is essentially the same as that used previously.

## MATERIALS AND METHODS

*Preparation of Pertussis "Toxin."*—The material for the cutaneous test was prepared by growing selected strains of H. pertussis at $p_H$ 8 on meat infusion broth containing 0.1 per cent soluble starch. The broth was put in a thin layer into a 2 liter Erlenmeyer flask and sterilized by steam at 20 pounds' (9 Kg.) pressure. Each flask of broth was heavily planted by using a forty-eight hour culture of H. pertussis on blood agar. The inoculated medium was incubated at 32 C. for four days in an atmosphere of 80 per cent oxygen and 20 per cent carbon dioxide. The growth from all good flasks of broth was pooled and passed through the Sharples centrifuge; then the clear fluid collected was passed through a Berkefeld filter and tested for sterility. The undiluted filtrate killed all mice given intravenous injections of 0.1 to 0.15 cc. and caused an area of necrosis of about 4 to 5 cm. in diameter when injected intradermally in rabbits. The "detoxified pertussis antigen" used in some of the experiments was prepared from pertussis "toxin" by detoxifying it with a 0.15 per cent concentration of solution of formaldehyde U. S. P. at 40 C. in eight days or less. The detoxified filtrate was preserved with a 1:10,000 dilution of merthiolate in physiologic solution of sodium chloride; it was completely nontoxic for rabbits and mice. In order to exclude nonspecific reactions a control broth was injected into all children at the site where cutaneous tests were performed. This control broth represented the liquid medium prepared as outlined but without inoculation with H. pertussis. Furthermore, pertussis "toxin" was heated in different ways and this material used as control for intracutaneous testing. The time of heating varied from ten to thirty minutes; the temperatures were between 56 C. and 70 C.

*Technic of Administration and Interpretation of Intracutaneous Tests.*—The flexor surface of the forearm was employed as the site of inoculation. One tenth cubic centimeter of the solution was injected intracutaneously to produce a wheal. The injected area was examined daily for three days or longer. A cutaneous test was not considered positive unless the reaction produced persisted for at least forty-eight hours. Nonspecific and traumatic reactions could be easily differentiated from specific ones by comparison with the results of the control test. A positive reaction consisted of the appearance after a latent period of several hours of swelling, redness and induration of the area of injection. A reaction which faded after twenty-four hours was not considered positive. Degrees of positiveness were denoted according to the extent of erythema and induration. A reaction

5. (*a*) Weichsel, M., and Douglas, H. S.: J. Clin. Investigation **16**:15, 1937. (*b*) Lapin, J.; Cohen, P., and Weichsel, M.: Arch. Pediat. **56**:590, 1939.

was considered: to be 1 plus (+) when an erythematous area measuring 10 mm. in diameter with little or no induration appeared; to be 2 plus (++) when the erythematous area measured 20 mm. in diameter and had slight induration; to be 3 plus (+++) when there was an area of deep erythema at least 25 mm. in diameter with considerable induration, and 4 plus (++++) when there was extensive induration with superficial epidermal necrosis and dusky erythema. A questionable reaction (+/—) was one having a definite area of erythema after twenty-four hours which was much diminished after forty-eight hours or one having considerable induration without erythema.

*Complement Fixation Test.*—The antigen used consisted of a suspension of H. pertussis grown on unadjusted Bordet agar and suspended in 50 per cent alcohol to which a 1 per cent solution of lecithin was added. The amount of lecithin used varied in each individual test, as has been outlined previously.[5a] In most experiments the addition of from 0.1 to 0.15 cc. of 1 per cent solution of lecithin to 1 cc. of the stock antigen gave the best results. In each positive case the serum was titrated, and the titers given in this paper are based on the dilution of serum.

TABLE 1.—*Results of Intradermal Tests with Pertussis Toxin Performed on Three Hundred and Sixty-Seven Healthy Children*

| | Children Under 1 Year | | Children 1 to 2 Years | | 3 to 6 Years | | Total | |
|---|---|---|---|---|---|---|---|---|
| Reaction | No. | % | No. | % | No. | % | No. | % |
| Positive | 7 | 17.1 | 16 | 16.5 | 45 | 19.6 | 38 | 18.5 |
| Doubtful | 3 | 7.3 | 12 | 12.4 | 24 | 10.5 | 39 | 10.6 |
| Negative | 31 | 75.6 | 69 | 71.1 | 160 | 69.8 | 260 | 70.8 |
| | 41 | | 97 | | 229 | | 367 | |

## RESULTS WITH INTRACUTANEOUS TESTS

Intracutaneous tests were performed on over 100 children who were either ill with whooping cough or who had recently recovered from the disease. Of these, only 90 patients could be used for statistical purposes. Another group of 416 children, used as controls, comprised 49 patients who were in the hospital convalescing from varicella or scarlet fever and 367 children treated in a clinic for the prophylaxis of whooping cough. All controls had a negative history of pertussis.

In evaluating results we took into consideration the age of the patient. The ages among those ill with whooping cough ranged from 3 months to 12 years. Most of them were between 9 months and 8 years of age. There were 13 children with active whooping cough under 1 year of age. Of these, 10 had positive intracutaneous reactions to testing. The ages of the children in the control group varied from 9 months to 7 years.

It was frequently difficult to determine the exact duration of the disease, since many patients were transferred from other institutions or came in without an accurate history. However, a fair approximation could be made. A large number of the children were not admitted

to the hospital until the disease had progressed well into the paroxysmal stage; consequently, the tests were frequently not performed early in the illness although we were particularly interested in determining how early in the disorder cutaneous sensitivity did occur. We tested 23 children who had a history of less than two weeks of illness. Of these, 11, or 47.8 per cent, had positive reactions. Of 36 children on whom intracutaneous tests had been performed by the twenty-first day of the disease, 21, or 58.5 per cent, reacted positively. Of the entire group of 90 there were 69, or 76.6 per cent, who had positive cutaneous reactions to pertussis "toxin" some time during the course of whooping cough. A few children showed negative cutaneous reactions until the fortieth or fiftieth day of illness. Several patients could not be tested before the fifth or sixth week of the disease, at which time they showed a strongly positive reaction. They might conceivably have had positive reaction by the twenty-first day of the disease.

TABLE 2.—*Results of One Hundred and Twenty-Two Tests with Pertussis Toxin Performed on Ninety Patients with Whooping Cough*

| Age | Number of Patients | Result of Intradermal Toxin Test | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | +/− | + | ++ | +++ | ++++ |
| Under 1 year | 13 | 4 | 2 | 5 | 4 | 3 | .. |
| 1 to 2 years | 30 | 15 | 6 | 6 | 10 | 6 | .. |
| 3 to 6 years | 32 | 8 | 7 | 9 | 10 | 6 | 1 |
| Older | 15 | 6 | 2 | 3 | 6 | 2 | 1 |
| Totals | 90 | 33 | 17 | 23 | 30 | 17 | 2 |

Activity of the disease was judged by the frequency and severity of paroxysms of cough and the occurrence of vomiting, cyanosis, convulsions and other complications. Severity of the disorder was rated from 1 to 4 plus, depending on the foregoing factor.

No correlation could be made between the activity of the disease and the intensity of the cutaneous reactions. Some of the children with the most severe involvement had negligible cutaneous reactions. Conversely, the cutaneous reaction was rarely suppressed in any definite form in those with severe proxysms.

Among the 367 children treated at the clinic for the prophylaxis of whooping cough, none of whom had a history of having had pertussis, 260, or 70.8 per cent, had negative cutaneous reactions. Tests were performed on 23 healthy children with a definite history of pertussis. Some of these patients had had the disease as long as seven years prior to the test. The reactions of 4 of these children were negative, of 2 doubtful and of 17 positive. Thus the percentage of positive reactions in this group is larger than in a corresponding control group of children with no known history of whooping cough.

The reactions to heated "toxin" although somewhat weaker than those to unheated "toxin" were not entirely negative. Heating the "toxin" for thirty minutes at 56 C. decreased its activity only slightly.

An attempt was made in many instances to establish a relation between the severity of the cutaneous reactions and the results of the complement fixation test. We had previously found that results of the complement fixation test are negative in about 90 per cent of normal children, irrespective of a previous history of pertussis. This observation is confirmed in the present study. We could not find any correlation in the group of normal children between the intensity of the cutaneous reaction and the result of the complement fixation test.

TABLE 3.—*Results of Intradermal Tests with Pertussis Toxin and of Complement Fixation Tests in Children with Positive Histories of Whooping Cough*

| Case No. | Time Elapsed Since Pertussis | Result of Cutaneous Tests | Result of Complement Fixation Tests | |
|---|---|---|---|---|
| 1 | 7 years | + | +++ | (1:10) |
| 2 | 6 years | ++ | ..... | ..... |
| 3 | 6 years | + | + | (1:30) |
| 4 | 6 years | + | ..... | ..... |
| 5 | 5 years | +/— | ++ | (1:10) |
| 6 | 2 years | + | ++ | (1:30) |
| 7 | 19 months | Negative | ..... | ..... |
| 8 | 1 year | + | ..... | ..... |
| 9 | 1½ years | + | Negative | ..... |
| 10 | 1 year | + | ..... | ..... |
| 11 | 4 years | ++ | ..... | ..... |
| 12 | 5 years | Negative | Negative | ..... |
| 13 | 5 years | + | ..... | ..... |
| 14 | 2 years | ++ | Negative | ..... |
| 15 | 9 months | + | +++ | (1:30) |
| 16 | 7 years | + | Negative | ..... |
| 17 | 3 years | Negative | ..... | ..... |
| 18 | 3 years | ++ | ..... | ..... |
| 19 | 5 years | ++ | ..... | ..... |
| 20 | 2 years | + | ..... | ..... |
| 21 | 3 years | Negative | ..... | ..... |
| 22 | 4 years | +/— | ..... | ..... |
| 23 | 7 months | ++ | ++++ | (1:30) |

Likewise, there was no correlation between the results of the two tests in the group of 90 children with active whooping cough. High as well as low titers of complement-fixing antibodies were found among patients with weak cutaneous reactions, as well as among those with strongly positive cutaneous reactions. There were 33 patients with active whooping cough who had positive reactions to the complement fixation test. The titers observed in some of these children were notable. In several patients, of varied ages, they reached 1:240! Some patients exhibited high titers toward the end of the second week of illness.

### DATA ON CHILDREN TREATED WITH ANTIGEN

Nine children with active whooping cough were given cutaneous tests and then injections intramuscularly of graded doses of "detoxified pertussis antigen," beginning usually with 0.5 cc. and increasing every

second day to 1 cc., to 2 cc., to 3 cc. and, in some cases, to 5 cc. The cutaneous tests were repeated in from ten to twenty days. In 8 of the 9 patients examined the intensity of the cutaneous reaction was definitely decreased, and in 1 it was unchanged after administration of the antigen. The reverse was found in children not treated with "detoxified pertussis antigen." These patients showed an increase in the intensity of their cutaneous reactions up to as long as fifty days from the onset of the illness. Furthermore, children treated with convalescent serum likewise showed an increase in cutaneous sensitivity. The results of the comple-

TABLE 4.—*Results of Intradermal Tests with Pertussis Toxin and of Complement Fixation Tests in Children with Whooping Cough*

| Case No. | Age | Severity of Disease, Grade | Day of Illness | Complement Fixation Test | | Cutaneous Test |
|---|---|---|---|---|---|---|
| | A. Children Not Treated with "Detoxified Antigen" | | | | | |
| 1 | 17 months | 4 | 17 | ..... | ..... | Negative |
| | | | 30 | +++ | (1:5) | Negative |
| | | | 40 | +++ | (1:20) | Negative |
| 2 | 3 years | 1 | 16 | ++++ | (1:150) | ++ |
| | | | 27 | +++ | (1:200) | +++ |
| 3 | 2 years | 3 | 23 | Not done | | Negative |
| | | | 36 | +++ | (1:20) | +/— |
| | | | 50 | ++++ | (1:30) | + |
| 4 | 2½ years | 1 | 60 | ++++ | (1:30) | +++ |
| 5 | 14 months | 2 | 23 | ++ | (1:30) | +++ |
| 6 | 7½ years | 2 | 40 | ++++ | (1:30) | +/— |
| 7 | 11 months | 2 | 14 | ++++ | (1:120) | +/— |
| 8 | 2 years | 3 | 22 | ++++ | (1:180) | ++ |
| 9 | 2 years | 1 | 21 | ++ | (1:15) | ++ |
| | B. Children Treated with "Detoxified Antigen" | | | | | |
| 1 | 2½ years | 1 | 13 | +++ | (1:20) | +++ |
| | | | 34 | +++ | (1:20) | +/— |
| 2 | 4½ years | 3 | 31 | ++++ | (1:240) | + |
| | | | 48 | ++++ | (1:180) | Negative |
| | | | 85 | +++ | (1:120) | .. |
| 3 | 5 years | 3 | 14 | ++++ | (1:180) | ++ |
| | | | 25 | ++++ | (1:60) | ++ |

ment fixation tests in this series did not differ materially from those obtained in nontreated control patients, as may be seen from table 5. It therefore appears that in patients treated with antigen likewise, no correlation exists between results of cutaneous tests and complement fixation tests.

We wished to study the way in which small doses of "detoxified pertussis antigen" injected intracutaneously would influence cutaneous sensitivity to pertussis toxin and the results of the complement fixation test. We selected 8 patients from our control group, children without whooping cough. They were in the hospital convalescing either from scarlet fever or varicella. Of these, 4 had a positive history of pertussis

and 4 did not. Cutaneous tests were given these patients, and blood was taken for the complement fixation test. After an interval of three days 0.2 cc. of "detoxified pertussis antigen" was injected intracutaneously. Three days later they received 0.3 cc. of antigen. Ten days after the initial cutaneous test and venipuncture the tests were repeated.

Examination of table 5 shows that 2 children of each group had an increase of cutaneous sensitivity, the others being unchanged. The result of the complement fixation test of the 2 patients in the first group was doubtful. A larger series of healthy children were given intra-

TABLE 5.—*Results of Cutaneous Tests and Complement Fixation Tests Following Intradermal Injection of "Detoxified Antigen" in Healthy Children*

A. Children with Negative History of Pertussis

| Case No. | Cutaneous Test | | Complement Fixation Test | |
|---|---|---|---|---|
| | Before Injection of Antigen | After Injection of Antigen | Before Injection of Antigen | After Injection of Antigen |
| 1 | +/− | +/− | Negative | Negative |
| 2 | +/− | +/− | Negative | Negative |
| 3 | + | ++ | + (1:30) | Negative |
| 4 | +/− | ++ | + (1:30) | +++ (1:10) |

B. Children with Positive History of Pertussis

| | Time Elapsed Since Pertussis | Intradermal Test | | Complement Fixation Test | |
|---|---|---|---|---|---|
| | | Before Injection of Antigen | After Injection of Antigen | Before Injection of Antigen | After Injection of Antigen |
| 1 | 7 years | + | ++ | Negative | ++++ (1:10) |
| 2 | 2 years | + | + | Negative | +++ (1:10) |
| 3 | 5 years | + | ++ | Negative | +++ (1:30) |
| 4 | 1 year | + | + | Negative | Negative |

cutaneous injections of pertussis "toxin" for prophylaxis. In the latter group the subsequent cutaneous reaction showed a slightly increased intensity in many instances, irrespective of a previous history of whooping cough. The remainder of these children showed no change in their cutaneous reactivity to pertussis "toxin." A retesting of these children was done after from six to twelve weeks. From table 5 it may be seen that the complement fixation test showed a marked increase in titer in 3 of 8 children. These patients had a history of having had whooping cough from two to seven years previously. Thus the intracutaneous injection of "detoxified pertussis antigen" raises the complement fixation ratio faster in children with than in those without a previous history of pertussis.

### PASSIVE TRANSFER EXPERIMENTS

In view of the allergic type of cutaneous sensitiveness elicited by pertussis "toxin" in patients with whooping cough, it seemed interesting to study the question of whether a local hypersensitivity to the toxic filtrate could be demonstrated using the Prausnitz and Küstner technic. In selecting suitable subjects for these experiments we tested children without any history of pertussis and used for the experiment those who failed to give positive cutaneous reactions. They received (on a specially marked area of the skin of the back) 0.1 cc. of pertussis convalescent serum or serum from patients with a strongly marked cutaneous reaction. Twenty-four hours later they were given a second injection of 0.1 cc. of a potent pertussis "toxin" which gave typical reactions in susceptible controls. All these experiments gave negative results. In no case could a local passive transfer be demonstrated.

In other patients the effect of mixtures of pertussis convalescent serums or of serum from children who gave a positive cutaneous reaction to pertussis "toxin" was examined. The results of these experiments were negative. In animal experiments, likewise, convalescent serum as well as animal pertussis antiserum failed to neutralize this "toxin."

### COMMENT

There is still disagreement about the nature of the toxin of H. pertussis. Bordet and Gengou [6] failed to demonstrate toxin in liquid cultures of pertussis bacilli. Teissier and his associates,[7] using Besredka's method, prepared toxin and titrated it by intradermal injection into guinea pigs and rabbits. Mishulow, Mowry and Scott [8] by means of the Shwartzman phenomenon showed that pertussis bacilli were capable of producing a toxic substance in culture filtrates and that vaccines containing this toxic substance stimulated formation of antibodies to a greater degree than those which lacked this toxic substance. Evans and Maitland [9] recently published results of experiments with a specially prepared pertussis toxin and demonstrated the extreme heat lability of at least the lethal factor. The filtrate which we employed during the present studies shows several characteristics of true extracellular toxins: we found symptoms of poisoning in animals after a period of incubation and lability of the toxin to heat and chemicals. Other properties, however, are lacking, for instance the capacity to produce neutralizing

6. Bordet, J., and Gengou, O.: Ann. Inst. Pasteur **20**:731, 1906; **21**:720, 1907; **23**:415, 1909.

7. Teissier, P.; Reilly, J.; Rivalier, E., and Cambessédès, H.: J. de physiol. et de path. gén. **27**:549, 1929.

8. Mishulow, L.; Mowry, I. W., and Scott, E. B.: J. Immunol. **19**:227, 1930.

9. Evans, D. G., and Maitland, H. B.: J. Path. & Bact. **45**:715, 1937.

antiserums in animals given injections of the toxin. However, absence of this ability is doubtful, since Demnitz, Schlüter and Schmidt [10] reported production of antitoxin in horses into which a highly active toxin had been injected. Another point which speaks against the theory of the filtrate's being a true exotoxin is the fact that relatively large amounts of it are necessary to kill animals.

The results of the intracutaneous injection of this toxic filtrate into human beings are interesting. Undoubtedly, the result of injection into children suffering or convalescing from whooping cough, an incidence of about 70 per cent of positive reactions, demonstrates the development of cutaneous hypersensitivity to the products of growth of H. pertussis. In several patients the change from a negative cutaneous reaction to a positive reaction could be observed during the course of the disease. This is in agreement with Toomey's findings.[11] He stated the belief that the organisms present in the disease-producing phase sensitize the patient ill with whooping cough and that such patients gradually become more sensitive to the toxic filtrate. The practical value of the test, however, is minimized by the fact that 18.5 per cent of healthy children without any history of pertussis likewise had positive reactions. In a certain number of this group there may have been an allergic type of response due to previous subclinical infections with H. pertussis. This seems likely, since some of these children had a positive reaction to the complement fixation test. In others the positive reaction may signify lack of protection comparable to that expressed by a positive Dick or Schick test in the absence of antitoxin. It seems that several fractions with different biologic activities are present in filtered broth, although the exact differentiation of them is still not completed. Furthermore, pertussis "toxin" as represented by our broth filtrates may act as a true antigen in eliciting the formation of specific antibodies. Intradermal injections of small amounts of "detoxified pertussis antigen," which is essentially the formaldehyde-treated broth filtrate employed for the cutaneous tests, definitely stimulated the production of complement-fixing antibodies. The fact that this effect seemed more pronounced in children with a history of pertussis is of interest. Weichsel and Douglas [5a] have shown that infection with H. pertussis following the injection of pertussis vaccines led to a considerable production of antibodies which represent a form of secondary stimulus in a previously vaccinated person.

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10. Demnitz, A.; Schlüter, W., and Schmidt, H.: Klin. Wchnschr. **15**:10, 1936.

11. (*a*) Toomey, J. A.: Mechanism of Whooping Cough, Am. J. Dis. Child. **56**:469 (Aug.) 1938. (*b*) Toomey, J. A., and Takacs, W. S.: J. Infect. Dis. **60**: 41, 1937.

The allergic nature of the cutaneous reactivity to pertussis "toxin" was confirmed by the results of the experiments on children with whooping cough, in which large doses of "detoxified pertussis antigen" were injected intramuscularly. The decrease in cutaneous sensitivity following these injections tends to indicate a desensitization to the specific allergic substance and may be of value if it parallels the general desensitization to pertussis "toxin." According to Toomey,[11a] the normal recovery from the disease is accompanied by a gradual desensitization to the toxic products.

The attempts to transfer passively cutaneous sensitivity to pertussis "toxin" to normal children proved unsuccessful. This particular type of bacterial allergy, like other forms of bacterial cutaneous sensitivity, does not seem to be based on the presence of circulating antibodies. The negative results of the neutralization experiments tend to confirm the theory of an allergic type of cutaneous reactivity.

No definite relation could be found between cutaneous reactivity and the results of the complement fixation tests. These experiments were undertaken on children with whooping cough as well as on healthy children. Although notable titers of complement-fixing antibodies were often observed in the group of children ill with pertussis even during early stages of the disease, the results of the cutaneous test proved to have no relation to the titers of antibodies found in the blood.

It is uncertain whether the allergic type of cutaneous response obtained in patients with whooping cough or those convalescing is significant in the development of immunity. It remains to be seen whether it will be possible to differentiate between allergic immune and allergic nonimmune persons by means of intracutaneous reactions.

## SUMMARY

A method for intracutaneous testing for susceptibility to whooping cough is presented with mode of preparation of pertussis "toxin," method of administration and interpretation of results.

In a group of 90 patients 69, or 76.6 per cent, had positive reactions some time during the course of the active disease. In a control group of 367 children with a negative history of pertussis 70.8 per cent had a negative, 10.6 per cent a doubtful and 18.5 per cent a positive cutaneous reaction. Seventeen of 23 healthy children with a positive history of whooping cough had positive cutaneous reactions, in some cases seven years after having had the disease.

A comparison of results of a test of cutaneous reactivity to pertussis "toxin" with those of a complement fixation test showed no definite correlation. Notable titers of complement-fixing antibodies were often observed, even during early stages of the disease.

Intramuscular injections of from 4 to 8 cc. of "detoxified pertussis antigen" in cases of active whooping cough definitely decreased the cutaneous sensitivity to pertussis "toxin," a fact which may be explained on the basis of desensitization in view of the apparently allergic nature of the cutaneous reaction.

Intracutaneous injections of small doses of "detoxified pertussis antigen" into healthy children caused an increase of the titer of complement-fixing antibodies, especially in those who had had the disease previously. Cutaneous sensitivity was either increased or unchanged.

The Prausnitz-Küstner experiment and neutralization tests gave negative results.

The complement fixation tests were performed by Dr. M. E. Roberts.

Lederle Laboratories, Inc., supplied the pertussis "toxin" used for the experiments as well as the "detoxified pertussis antigen."

# DISTURBANCES OF HEPATIC FUNCTION IN ICTERUS GRAVIS

## REPORT OF TWO CASES

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Icterus gravis neonatorum is a descriptive term for a clinical syndrome which may be the expression of a variety of pathologic processes. Aside from the symptomatic examples of known cause the interpretation of postmortem observations in regard to pathogenesis presents a problem in each given case and cannot be applied safely to other cases as long as the etiology of the "idiopathic" types remains unknown. Especially the evaluation of changes in the parenchyma of the liver offers difficulties, because of considerable differences in the pictures described by various observers. In many reports the presence of hemopoietic foci is given prominence, while alterations in the parenchymal cells are treated casually. Occasionally the liver has been described as normal, but most authors have reported acute and sometimes severe changes in the polygonal cells. Such lesions deserve particular attention in cases in which excessive hemolysis does not account for the icterus or in which hemopoietic foci in the sinusoids are lacking. The development of chronic lesions, necessarily dependent in part on the period of survival beyond the neonatal phase of the disease, has also been reported. Hawksley and Lightwood [1] observed varying degrees of fibrosis in the liver in 7 of 9 infants with icterus gravis neonatorum surviving beyond the age of 5 weeks and pointed out that icterus gravis has to be considered among other possible factors in the etiology of cirrhosis of the liver in infancy. Conversely, several cases of infantile cirrhosis have been reported in which the past history revealed severe or prolonged neonatal icterus.[2]

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From the Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute.

1. Hawksley, J. C., and Lightwood, R.: Contribution to Study of Erythroblastosis: Icterus Gravis Neonatorum, Quart. J. Med. **3**:155 (April) 1934.

2. (*a*) Bossert, O.: Zur Frage der Leberzirrhose im Säuglingsalter, Monatschr. f. Kinderh. **14**:174, 1916. (*b*) Braid, F., and Ebbs, J. H.: Atrophic Cirrhosis of Liver Following Icterus Gravis Neonatorum, with Pathological Report, Arch. Dis. Childhood **12**:389 (Dec.) 1937. (*c*) Curtiss, C. C.: Juvenile Cirrhosis of Liver, with Report of Case, Arch. Pediat. **51**:396 (June) 1934. (*d*) Hanau, F.: Beitrag zur Kenntnis der hepato-lienalen Systemerkrankung, Monatschr. f.

*(Footnote continued on next page)*

These observations tend to emphasize the importance of hepatic damage in certain cases of icterus gravis neonatorum. The 2 cases of icterus gravis from one family reported here are outstanding examples in point. One illustrates a protracted course resulting in cirrhosis and the other an acute phase of hepatic damage, both associated with an unusual derangement of carbohydrate metabolism on the basis of hepatic dysfunction, which is rarely observed in infants.

## REPORT OF CASES

CASE 1.—*History.*—W. H., an 8 month old white boy, was admitted to the Children's Memorial Hospital in February 1939, because of failure to gain weight. The temperature had been elevated for the previous ten days.

The family history was noncontributory. Both parents were in good health. The mother's first pregnancy in 1935 had resulted in the birth of a healthy child who had never been jaundiced and had remained well. There had been no miscarriages. Jaundice, diabetes mellitus or disease of the blood was not known to have occurred on either side of the family. The Wassermann reaction of the blood of both parents was negative.

The second pregnancy was uneventful, and the patient was delivered normally at term. There was no discoloration of the vernix caseosa, and the placenta appeared normal on gross inspection. The infant weighed 6 pounds and 14 ounces (3,118 Gm.) at birth, had a lusty cry and seemed normal in every respect. On the sixth day of life the child became listless and took his feedings poorly. At this time intense jaundice was noted. It lasted until the child was 18 days old. The liver and spleen were first noted to be enlarged on the twenty-first day. The stools were always well colored.

The first examination of the blood was made on the eleventh day and showed 120 per cent hemoglobin (Sahli) and 5,670,000 erythrocytes and 20,600 leukocytes per cubic millimeter. The differential count was not unusual. No nucleated red blood cells were found on the smears. The fragility test revealed beginning hemolysis at a concentration of 0.44 per cent sodium chloride and complete hemolysis at 0.36 per cent. On the fourteenth day the hemoglobin content was 110 per cent, with 4,900,000 erythrocytes per cubic millimeter.

The infant continued to be listless and ate poorly. He gained weight slowly and unsatisfactorily in spite of many attempts to improve his formula. Orange juice and cod liver oil were given in ample amounts. At the age of 3 months he weighed 8 pounds and 7 ounces (3,827 Gm.) and was pale. The liver was palpable 3 fingerbreadths below the costal margin and the spleen 2 fingerbreadths below. Examination of the blood at this time showed 72 per cent hemoglobin and 3,120,000 erythrocytes per cubic millimeter. After repeated intramuscular injections of small doses of maternal blood, the anemia improved temporarily, but the enlargement of the liver and spleen became more marked. The infant was susceptible to infections of the respiratory tract and had occasional episodes of vomiting and diarrhea. Ten days before admission an intermittent fever with a temperature up to 103 F. developed. A few days later the child began to cough.

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Kinderh. **29**:54, 1924. (*e*) de Lange, C.: Zur Leberzirrhose im Säuglingsalter, ibid. **14**:351, 1918. (*f*) Sobel, I. P., and Zucker, J. M.: Icterus Gravis Neonatorum: End Results of the Syndrome of Nuclear Jaundice, J. Pediat. **16**:445 (April) 1940. (*g*) Webster, R.: Pathological Reports from the Children's Hospital, Melbourne: Juvenile Cirrhosis of Liver, M. J. Australia **2**:246 (Oct. 1) 1938.

*Physical Examination.*—On admission the infant appeared poorly developed and undernourished but in no distress. The skin and mucous membranes were pale but not icteric. The teeth had not erupted. There was beading of the ribs. The frontal and parietal bones were somewhat prominent. The veins over the wall of the chest were distended. Bronchovesicular breathing and rales were heard in several areas over the lungs. The liver was markedly enlarged and firm. The spleen was palpable 1 cm. below the margin of the ribs. There was no clinical evidence of ascites. The temperature was 100.6 F.

*Laboratory Tests.*—The reaction of the urine was acid; there was a 1 plus reaction for albumin; the test for sugar gave a 4 plus reaction, and there was no acetone or diacetic acid. A blood count showed 54 per cent hemoglobin and 2,930,000 red blood cells and 24,000 white blood cells per cubic millimeter, with 77 per cent polymorphonuclear leukocytes. Chemical examination showed 19 mg. of nonprotein nitrogen and 174 mg. of sugar (determined by the method of Folin-Wu), carbon dioxide–combining power 38.6 volumes per cent, 14.3 mg. of serum calcium and 4.5 mg. of phosphorus per hundred cubic centimeters.

*Course.*—The child was given a similac formula and dextrose water between meals. Treatment with insulin was begun at once. Individual doses ranged from 2 to 5 units, the total being increased gradually to 18 units per day. The urine continued to reduce Benedict's solution. Ketone bodies were not found in the urine at any time. On the third day the blood sugar was found to be 223 mg. per hundred cubic centimeters. For a few days the temperature was irregularly elevated; then it became subnormal and remained so except for a marked terminal elevation. On the eighth day the child began to have convulsive movements of the upper extremities. It was noted that the skin became ashen gray and the child perspired a great deal. This condition would change rapidly, for at other times the skin was dry and flushed. During one of the convulsive seizures the sugar content of the blood was determined and was found to be 134 mg. per hundred cubic centimeters. The patient died on the tenth hospital day.

*Necropsy.*—The postmortem examination was made two hours after death. The following abstract lists the outstanding observations: The body measured 61 cm. in length and weighed 10 pounds (4,536 Gm.). The skin was white and clear. There was no edema. A small amount of greenish, mucoid exudate was present in the left nostril. There was marked pallor of the mucous membranes. No erupted teeth were present. Moderately distended veins extended symmetrically from both sides of the abdomen along the wall of the chest. The abdominal wall was relaxed. The liver was palpable as a firm, finely granular organ extending to the iliac crest. The spleen was palpable 1 fingerbreadth below the margin of the ribs. There was slight beading of the costochondral junctions. Small discrete lymph nodes were palpable in the posterior cervical and inguinal regions.

Peritoneal Cavity: There was no free fluid or adhesions. The situs of the abdominal organs was not unusual except for a malrotated cecum.

Lungs: The combined weight was 105 Gm. (normal, 97 Gm.[3]). There were multiple, sharply defined, slightly prominent areas of bronchopneumonia scattered through all the lobes. On cut surface these areas stood out as dark, meaty, well defined foci, averaging 1 to 1.5 cm. in diameter. The bronchi contained a small amount of thin, foamy fluid.

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3. The normal weights quoted for comparison are taken from Coppoletta, J. M., and Wolbach, S. B.: Body Length and Organ Weights of Infants and Children, Am. J. Path. **9**:55 (Jan.) 1933.

Spleen: The spleen weighed 32 Gm. (normal, 20 Gm.). It was fairly firm, smooth, reddish brown and of the usual shape. On the cut surface the parenchyma was somewhat glassy and reddish brown. The malpighian follicles were indistinct. Grossly no increase in fibrous tissue was noticeable.

Pancreas: The pancreas weighed 20 Gm. It was of the usual shape and did not appear enlarged or otherwise abnormal. The pancreatic duct was dissected, and nothing unusual was found.

Liver: The liver weighed 400 Gm. (normal, 254 Gm.). It was large, firm and pale yellow. The surface was finely granular, with regular, slightly elevated polygonal areas averaging 2 mm. in diameter, separated by slightly depressed, delicate, hairlike, reddish gray bands of tissue. The capsule was thin and translucent. The resistance to cutting was moderately but distinctly increased. The appearance of the cut surface was essentially the same as that of the outer surfaces. Only small amounts of blood escaped when the organ was cut. The gallbladder and the extrahepatic bile ducts appeared normal.

Heart, Kidneys, Adrenals, Brain and Pituitary: The remainder of the organs were not remarkable as regards weight and gross appearance.

*Microscopic Examination.*—Lungs: Most of the alveoli were filled with a cellular exudate consisting mainly of polymorphonuclear leukocytes and a smaller number of large macrophages suspended in a pale, serum-like material. The pneumonic foci usually followed lobular outlines. In other areas there was considerable infiltration of the alveolar septums with mononuclear and polymorphonuclear cells, while the alveolar lumens were empty. In some fields the alveolar walls were thinned out and occasionally ruptured. Fairly severe toxic changes were present in the lymphoid follicles encountered frequently along the course of the bronchi. Such changes consisted in the presence of large macrophages, hyaline, amorphous masses and nuclear fragments.

Spleen: The malpighian corpuscles were numerous and fairly large but depleted of lymphocytes. Mild toxic changes were found in the secondary centers. The sinusoids were as a rule empty. The cells of the endothelial lining had fairly large, rounded, prominent nuclei. Some large macrophages found in the cords of Billroth contained a finely dispersed brown pigment which gave a negative reaction for iron. There was no increase in fibrous tissue.

Pancreas: Six sections were stained with hematoxylin and eosin, and several sections were stained with aniline blue and Bensley's stain. The architecture of the pancreas was well preserved. Except for a mild edematous widening of the interlobular and interacinar connective tissue, the sections were not remarkable. The islets of Langerhans were present in adequate numbers in every section. The size of the individual islets varied within normal limits. Within them no fibrosis was observed. The aniline blue stain permitted differentiation between three types of cells, those with bright red, distinct cytoplasmic granules constituting approximately 20 per cent and those with an indistinct, grayish blue cytoplasm without definite granules accounting for most of the remaining cells except for rare polyhedral cells with darker blue cytoplasm and a suggestion of granules. The ducts and blood vessels were not remarkable.

Liver: Sections were fixed in Zenker's fluid, absolute alcohol and formaldehyde and stained with hematoxylin and eosin, Best's carmine and scarlet red, as well as with Prussian blue and Mallory's aniline blue. There was marked distortion of the hepatic architecture. The parenchyma was divided into irregular fields by bands of connective tissue running between the portal areas. Within the lobules the central veins occupied an eccentric position and were distended (fig. 1).

The radial arrangement of the liver cells in regular cords was completely lost. The cells formed blocks, sheets, irregular groups and alveolar or tubular structures. These peculiar tubules were composed of large typical liver cells surrounding a lumen, from which they were separated by a cuticular condensation of their cytoplasm. The lumens were empty. Septums of connective tissue radiated into the lobular fields. The sinusoids were mostly compressed beyond recognition. Only in a few areas were they dilated. The reticular pattern was greatly distorted throughout. The liver cells varied in size. The cytoplasm was pale and finely granular. Many cells had large eccentric vacuoles. The borders of the cells were distinct. Toward the periphery of the lobules the character of the cells changed: They grew smaller, the cytoplasm was less granular; the nuclei stained more lightly, and the cells resembled those of the bile ducts, especially when arranged in a tubular pattern. The number of bile ducts was greatly increased. Numerous narrow, empty tubules extended from the periportal space toward the lobules. The periportal connective tissue was distinctly increased and contained small round cells with dark nuclei of somewhat irregular shape. Here and there small foci of polymorphonuclear infiltration were found. There was no evidence of hemosiderosis.

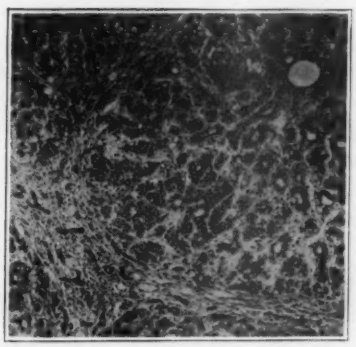

Fig. 1 (case 1).—The liver. Note distortion of architecture, increase in fibrous tissue about portal tracts and between liver cells and increase in number of bile ducts (low power; hematoxylin and eosin).

In a section stained with Best's carmine the central, more voluminous cells contained heavy granules of glycogen. The peripheral cells, apparently newly formed, contained only a little finely distributed glycogen or none at all. The nuclei were free from glycogen throughout. The granules of glycogen in the cytoplasm were usually concentrated on one side of the cell, but a number of cells were found in which the entire cytoplasm was filled with red granules. In addition to the glycogen some cells contained large eccentric vacuoles which when stained with scarlet red showed the presence of fat. In contrast to the glycogen, the fat was distributed mainly through the periphery of the lobular fields, although this was not a constant feature, and the terms "peripheral" and "central" applied not to the normal but to the distorted hepatic lobules. The few patent sinusoids contained a few red blood cells. The Kupffer cells were not remarkable.

Kidneys: A number of cells in the loops of Henle were found to contain small or medium-sized droplets of glycogen.

Adrenals: The scarlet red stain revealed no appreciable depletion of lipids. The hematoxylin-eosin sections were not remarkable.

Pituitary: The aniline blue stain brought out the various types of cells of the anterior lobe in apparently normal proportions. The pars intermedia contained a few tubular structures. One to two rows of basophil cells were present in the pars nervosa adjacent to the anterior lobe. Farther posteriorly there was no basophilic invasion.

Ribs: Throughout the zone of cartilage proliferation islands of loose, young, vascular connective tissue were found. The columns of degenerating cells of cartilage were lengthened and slightly irregular. The capillary penetration was uneven. Marrow elements extended directly up to the epiphyseal line. The bony spicules of the shaft often had narrow seams of osteoid. The bone marrow was actively hemopoietic. The proportions of leukopoietic and erythropoietic and mature and immature cells did not appear disturbed.

Brain: Sections from the cortex, corpus striatum, thalamus, hypothalamus, cornu ammonis, dentate nucleus, pons and medulla were examined. The outstanding feature common to all the sections was marked edema, demonstrable by the considerable widening of the perivascular spaces of His, which appeared empty except for fine radial stringy fibers running from the adventitia to the

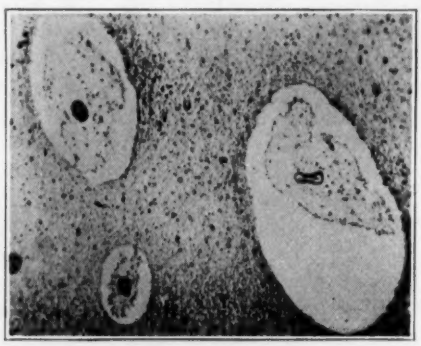

Fig. 2 (case 1).—The brain. Cystic spaces in the white matter of the cerebral hemisphere (low power; Mallory's phosphotungstic acid and hematoxylin).

surrounding nervous tissue. In the white matter underlying the cortex there were numerous fairly wide cystic spaces of round or elongated shape. Concentric condensations of glial fibers surrounded these cysts, but there was no concentration of glial cells in their environment. Most of these spaces contained an eccentrically located blood vessel surrounded by loose tissue formed by proliferated adventitial cells (fig. 2). Occasionally extravasated fresh red blood cells in small numbers were found in this loose tissue, more rarely in the free cystic space, which was otherwise empty. The pyramidal cells of the cortex were markedly diminished in number and small, usually shrunken with pyknotic nuclei and darkly staining, sometimes finely vacuolated cytoplasm. The layers were indistinct, and there was a diffuse, irregular increase in glial cells. Equally striking were the changes in the corpus striatum where a number of vessels were surrounded by circular hemorrhages forming a coat within the Virchow-Robin spaces. Only rarely was there an extravasation beyond the adventitia into the spaces of His or into the tissue itself. The perivascular edema in this region was so intense that the tissue in the neighborhood of blood vessels often assumed a grossly vacuolated, honeycombed appearance. The large ganglion cells were pale but not appre-

ciably diminished in number. Occasionally there was fusion of two neighboring cells. The nuclei were as a rule intact, but sometimes the nucleolus had disappeared, and in several instances the nuclear membranes were fading. Some cells were recognizable only as pale cytoplasmic masses or shadows. Pseudoneuronophagia was seen here and there, but actual neuronophagia was not observed. There was no appreciable loss of ganglion cells in the cornu ammonis or in the dentate nucleus of the cerebellum. The sections of the pons and medulla were not remarkable except for shrinking and pyknosis of the nuclei in some cell groups. In the hypothalamus there was diminution of ganglion cells, with focal increase in glial fibers.

*Anatomic Diagnoses.*—The diagnosis was: biliary (intralobular) cirrhosis of the liver; splenomegaly; anemia; rickets; cerebral edema; local cortical gliosis; multiple cysts in the cerebral white matter; perivascular petechiae; acute ganglion cell damage; bronchopneumonia, and malrotation of cecum.

*Postmortem Bacteriologic Studies.*—There was no growth in cultures of material from the spleen, lungs and spinal fluid. No organisms were seen on direct smears.

*Postmortem Chemical Determinations.*—Examination of blood from the heart (taken for chemical studies immediately after opening the thoracic cavity, i. e., approximately two hours and fifteen minutes after death) showed: 66.6 mg. of sugar, 40 mg. of nonprotein nitrogen, 86 mg. of cholesterol, 3 Gm. of serum protein (2.02 Gm. albumin and 0.98 Gm. globulin) and 2 Gm. of total lipoids per hundred cubic centimeters.

The spinal fluid (removed by lumbar puncture approximately three hours after death) contained 74 mg. of sugar per hundred cubic centimeters.

Fifty grams of liver was submerged in potassium hydroxide two hours and thirty minutes after death, and the glycogen content was determined. In the process of filtration an undetermined quantity was lost. The final reading was 620 mg. per hundred grams. The liver, with a total weight of 400 Gm., therefore contained a minimum of 2.48 Gm. of glycogen.

*Summary.*—This patient presented the clinical picture of icterus gravis without erythroblastosis. After the neonatal period, cirrhosis of the liver and anemia developed, together with a pseudodiabetic picture which insulin failed to influence. Before death insulin-like reactions were observed in the absence of hypoglycemia. At autopsy, besides cirrhosis of the liver, widespread anatomic lesions were found in the brain.

CASE 2.—*History.*—The infant brother of the preceding patient was born at term in January 1940, nineteen months after the birth of the first patient. The mother had been under close supervision during pregnancy, but nothing unusual had been noticed. Delivery was normal. The birth weight was 6 pounds and 11 ounces (3,033 Gm.). The child had a good color, cried spontaneously and nursed well. The physical examination after birth revealed nothing abnormal. On the fourth day the skin and the mucous membranes became deeply icteric, and pitting edema developed over the lower half of the body. The child now became listless, nursed poorly, regurgitated his feedings and had a weak cry. On the fifth day the liver and spleen became palpable. The stools were always well colored. The urine became dark after the fourth day. On the fifth day examination of the blood showed: 130 per cent hemoglobin (Sahli) and 5,630,000 erythrocytes and 11,400 leukocytes per cubic millimeter, with a differential count of 59 per cent polymorphonuclear leukocytes, 34 per cent lymphocytes, 5 per cent mononuclear leukocytes, 1 per cent eosinophils and 1 per cent basophils. A blood culture remained sterile. The fragility test showed beginning hemolysis in a 0.40 per cent

and complete hemolysis in a 0.30 per cent solution of sodium chloride. The urine was dark and alkaline and contained albumin. Six drops reduced Benedict's solution.

On the fifth and sixth days the amount of hemoglobin and the red blood cell count were slightly higher. The reaction for sugar in the urine became even more strong. The child became limp and had periods of cyanosis with shallow respirations. At times slight twitchings of the face and arms were noted. On the seventh day the blood sugar was found to be 131 mg. per hundred cubic centimeters. Insulin was given in increasing amounts during the following twenty-four hours. Beginning with 1 unit, the dosage was increased to 8 units, the total amounting to 15 units. The urine continued to reduce Benedict's solution. After the administration of insulin the convulsive twitchings became more marked and the periods of cyanosis more frequent and prolonged. The temperature was always within normal limits. Fifty cubic centimeters of a 5 per cent solution of dextrose was given subcutaneously with the last dose of insulin, but the infant died on the eighth day of life.

*Necropsy.*—The postmortem examination was performed ten hours after death at an undertaker's parlor. Only the pertinent findings are given. The body was well developed and fairly well nourished. The skin and mucous membranes were deeply icteric. There was slight nonpitting edema in the region of the hips. A yellow mucoid exudate was present in the right nostril. Bright red blood oozed from the left nostril. The umbilicus was dry and clean. The umbilical cord was a dry, black stump of 8 mm. The liver was palpable 3 fingerbreadths below the costal margin. The skeleton was not remarkable except for moderate overriding of the cranial bones.

Peritoneal Cavity: There was 3 cc. of clear deep yellow fluid. The liver descended 3.5 cm. beyond the costal margin in the midclavicuiar line; the spleen, 1 cm. in the left anterior axillary line.

Lungs: The lungs were heavy, firm, icteric and mottled with dark hemorrhagic confluent areas. Crepitancy was absent except in the anterior portions. The bronchial mucosa was icteric.

Spleen: The weight of the spleen was estimated at 15 to 20 Gm. The organ was dark purple and moderately firm. The markings on the cut surface were indistinct.

Gastrointestinal Tract: There were streaky patches of an ochre yellow pigment in the mucosa of the lower part of the esophagus, the stomach and the duodenum. The mucous membrane of the stomach was edematous. The ampulla of Vater in the duodenum was well developed. The duodenal mucosa was hyperemic and edematous. Throughout the small intestine numerous confluent and petechial hemorrhages were found in the mucosa.

Liver: The weight of the liver was estimated at 250 Gm. The organ was moderately firm, smooth and light brownish yellow. The markings were slightly accentuated. The gallbladder contained 1 to 2 cc. of bile-stained mucus. The extrahepatic bile ducts were patent to probing and not unusual in distribution. The portal vein was not remarkable except for bile staining of the intima.

Heart, Kidneys, Pancreas and Bladder: These organs were icteric but not otherwise grossly abnormal. The bladder contained approximately 10 cc. of dark brown urine. The marrow of the ribs, femur and vertebrae was dark, brownish red and dry.

Brain: The external appearance was not unusual; the color of the fresh specimen was pale pink. The spinal fluid was clear and colorless. There were no

hemorrhages. Coronal sections after fixation revealed intense symmetric icteric staining of the posterior portion of the lentiform nucleus, the thalamus, the subthalamic region, the cornu ammonis, the dentate nucleus and the flocculus of the cerebellum, the dorsal layers and the olives of the medulla oblongata and the gray matter throughout the spinal cord.

*Microscopic Examination.*—Lungs: The alveoli were filled with red blood cells, polymorphonuclear leukocytes and in some places serum-like fluid. A few keratinized epithelial cells were found in some places. There was marked engorgement of the pulmonary capillaries. Nucleated red blood cells were not seen in the vessels.

Spleen: The architecture was preserved. The malpighian follicles were numerous and distinct. The red pulp was congested. Moderate numbers of normoblasts were found loosely distributed through the reticulum. These cells did not form definite foci, and their number did not appear increased. There were also occasional undifferentiated hemopoietic cells. The sinusoids contained a few large phagocytic cells laden with a brown pigment which did not give the reaction for iron. The sections contained hardly any hemosiderin.

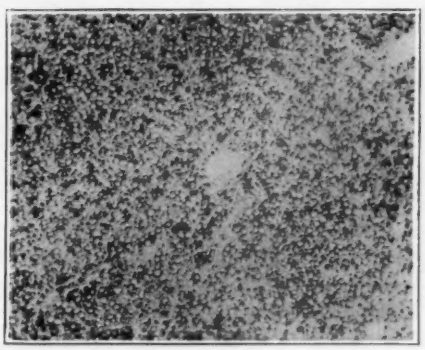

Fig. 3 (case 2).—The liver. Note severe fatty changes (low power; hematoxylin and eosin).

Pancreas: The interstitium was somewhat edematous, but the amount of fibrous tissue was not increased. The acinar elements were well preserved. The islets were abundant and of appropriate size. No degenerative or inflammatory changes were demonstrable.

Liver: The architecture of the liver was basically preserved but markedly obscured by swelling and vacuolation of the polygonal cells (fig. 3). Usually a narrow rim of stainable cytoplasm was present, and the nucleus was displaced and flattened or had disappeared. The large vacuoles were filled with fat. At the periphery of the cells droplets of bile pigment were frequently found. The intracellular and intercellular bile capillaries were distended with thrombus-like masses of bile. Practically no glycogen was found in sections stained with Best's carmine. The sinusoids were compressed by the large liver cells. The Kupffer cells were swollen and laden with hemosiderin.

At the periphery of the lobules short, narrow tubular structures, the cells of which were free from fat or pigment, were seen. There was no increase in fibrous tissue. The portal spaces were mildly infiltrated with lymphocytes and a few pyknotic nuclei resembling those of normoblasts. There were, however, no definite foci of hemopoiesis either here or in the sinusoids.

Bone Marrow: The marrow was moderately cellular. Mature cells of the granulocytic series were extremely rare. Only a few myelocytes were found. Because of this diminution of granulocytes there was a relative preponderance but not an absolute increase of the erythropoietic elements. Most of these were young forms. Approximately 50 per cent of all cells were undifferentiated forms with a basophilic cytoplasm and round or kidney-shaped nuclei, with unevenly distributed chromatin and fairly heavy nuclear membranes. The megakaryocytes were slightly increased in number. Numerous large cells with small pyknotic nuclei and voluminous cytoplasm were diffusely laden with hemosiderin.

Brain: There was some patchy fibrous thickening of the arachnoid. The pia mater was mildly infiltrated with mononuclear cells. There was no evidence of damage to the cerebral cortex. In the hippocampus there were widespread fragmentation of the tissue and severe damage to many ganglion cells of the fascia dentata. The cytoplasm of these cells stained a more or less deep pink with hematoxylin and eosin; the nuclei were fading or had disappeared, and the cell borders were indistinct. Some cells were recognizable only as faint shadows. In the globus pallidus similar changes were encountered, and in addition many cells were swollen. The most extensive cellular damage was found in the dentate nucleus of the cerebellum, where many pale shadows were seen. However, even here a great many ganglion cells were intact. The same was true for the spinal cord, where there was much less damage to the ganglion cells than would be expected from the extent of gross staining of the gray matter. The Purkinje cells of the cerebellum were somewhat pale but otherwise well preserved. In general the areas of gross pigmentation were somewhat fragmented, but there was no appreciable proliferation of glial cells. In a few areas of the cerebellar white matter there were small perivascular hemorrhages, and there was distinct proliferation of adventitial cells around the medium-sized and larger blood vessels.

Anatomic Diagnoses: The conditions included were icterus gravis; steatosis and hemosiderosis of the liver; splenomegaly; nuclear icterus of the brain and hemorrhagic (aspiration) bronchopneumonia.

*Postmortem Urinalysis.*—Examination of the urine showed a 4 plus reaction for albumin, a 4 plus reaction for sugar, a 4 plus reaction for bile and no acetone or diacetic acid. The sediment contained many red blood cells.

*Postmortem Chemical Determinations.*—Examination of the blood at The Children's Memorial Hospital thirteen hours after death showed: 137 mg. of sugar, 56 mg. of nonprotein nitrogen, 128 mg. of plasma cholesterol and 415 mg. of plasma chlorides per hundred cubic centimeters, and an icteric index of 77. The direct van den Bergh reaction was negative and the indirect reaction strongly positive.

*Summary.*—In this newborn infant, a brother of the first child, symptoms of icterus gravis developed on the third day and were associated with insulin-refractory hyperglycemia and glycosuria. Erythroblastosis and anemia were absent. Convulsions occurred toward the end of the first week of life and seemed to be aggravated after insulin therapy. The patient died on the eighth day. The autopsy revealed severe fatty changes, hemosiderosis and bile stasis in the liver and extensive nuclear icterus of the brain.

## COMMENT

The diagnosis of atypical forms of diseases of unknown etiology is often a difficult problem. As new case reports are added to the classic descriptions, the original criteria may prove too strict.

This has been true of icterus gravis and the closely related conditions of hydrops foetalis and anemia of the newborn. The very criterion which led to the grouping of these diseases under the common term of erythroblastosis had to be abandoned. The etiologic relation of the three syndromes, suggested notably by Diamond, Blackfan and Baty,[4] cannot be doubted; but on the basis of adequate case studies [5] the view is now widely accepted that neither the presence of excessive numbers of circulating nucleated red blood cells nor the demonstration of abnormal extramedullary hemopoiesis is essential for the diagnosis of icterus gravis. It has also become evident that the early onset of symptoms is not a strict diagnostic requirement. In a patient reported on by Ross and Waugh [6] the icterus was first observed at the age of 4 days. Hoffmann and Hausmann [7] noted the beginning of icterus at the age of 5 days

4. Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, J. Pediat. **1**:269 (Sept.) 1932.

5. (*a*) Altzitzoglou, J.: Das Blutbild beim Icterus neonatorum familiaris gravis und seine diagnostische Bedeutung, Monatschr. f. Kinderh. **58**:329, 1933. (*b*) Arondel, A.: Ictère grave familial du nouveau-né sans érythroblastose, Bull. Soc. de pédiat. de Paris **36**:670 (Nov.) 1938. (*c*) Astrachan, M.: Jaundice in Children: Report of Six Cases of Icterus Gravis Neonatorum, Am. J. Dis. Child. **53**:541 (Feb.) 1937. (*d*) Cohen, P.: Anemia of Newborn and Erythroblastosis—Are They Inseparable? J. Pediat. **7**:220 (Aug.) 1935. (*e*) Greenwald, H. M., and Messer, W.: Icterus Neonatorum Gravis: Report of Case Which Recovered with Sequelae Pointing to Involvement of the Central Nervous System, Am. J. M. Sc. **174**:793 (Dec.) 1927. (*f*) Hart, A. P.: Familial Icterus Gravis of New-Born and Its Treatment, Canad. M. A. J. **15**:1008 (Oct.) 1925. (*g*) de Lange, C.: Kernikterus (Orth-Schmorl) mit und ohne Erythroblastose, Jahrb. f. Kinderh. **145**:273, 1935; Kernicterus in Familial Icterus Gravis Without Noticeable Erythroblastosis, Maandschr. v. kindergeneesk. **8**:257 (April) 1939. (*h*) Miller, H. C.: Familial Occurrence of Icterus Gravis, Congenital Anemia of Newborn and Erythroblastosis Fetalis, Yale J. Biol. & Med. **11**:363 (March) 1939. (*i*) Montlaur, J. H., and Levy, P. P.: Ictère grave familial du nouveau né. Absence d'érythroblastose sanguine et viscérale, Bull. Soc. de pédiat. de Paris **35**:598 (Nov.) 1937; Ictère grave familial du nouveau-né. Erythroblastose transitoire, anasarque, mort, ibid. **36**:673 (Nov.) 1938. (*j*) Parsons, L. G.; Hawksley, J. C., and Gittins, R.: Studies in Anaemias of Infancy and Early Childhood: Haemolytic (Erythronoclastic) Anaemias of Neonatal Period, with Special Reference to Erythroblastosis of New Born, Arch. Dis. Childhood **8**:159 (June) 1933. (*k*) Péhu, M.; Noël, R., and Brochier, A.: Sur des cas d'ictère familial du nouveau-né avec guérison après traitements, Bull. Acad. de méd., Paris **117**:375 (March 23) 1937. (*l*) Saxl, O.: Icterus gravis und kongenitale Anämie, Jahrb. f. Kinderh. **148**:271, 1937. (*m*) Zimmerman, H. M., and Yannet, H.: Kernikterus: Jaundice of Nuclear Masses of Brain, Am. J. Dis. Child. **45**:470 (April) 1933.

6. Ross, S. G., and Waugh, T. R.: Certain Types of Icterus Gravis, Am. J. Dis. Child. **51**:1059 (May) 1936.

7. Hoffmann, W., and Hausmann, M.: Icterus neonatorum gravis, Monatschr. f. Kinderh. **33**:193, 1926.

in 1 of their patients. Boehncke [8] reported the onset of icterus on the twelfth day in 1 of his patients, and Hawksley and Lightwood [1] in their study on icterus gravis included a child in whom icterus was first noted during the third week.

Apart from the late onset, the clinical manifestations in case 1 were typical enough: profound and prolonged icterus, somnolence and enlargement of the liver and spleen, followed by pallor and anemia. Other causes of severe neonatal icterus, such as premature birth, congenital syphilis, the various forms of neonatal sepsis, malformation of the bile ducts and congenital acholuric jaundice, can be excluded. The diagnosis was confirmed by the subsequent occurrence of icterus gravis with kernicterus in the patient's brother (case 2), in whom nearly all the classic signs of the disease, including edema, were present.

The pathogenesis of jaundice in icterus gravis neonatorum is still far from clear. Ylppö,[9] in 1918, on the basis of the then prevailing conception of the production of bile pigment by the liver cells, considered the icterus as purely hepatic in nature. Today it is the consensus that both hemolysis and absolute or relative hepatic insufficiency are factors. In the terminology of Rich,[10] icterus gravis would be a combination of retention and regurgitation jaundice. The factor of hemolysis was stressed particularly by those who, like Parsons, Hawksley and Gittins [5j] and Lehndorff,[11] considered icterus gravis as a manifestation of a hemolytic type of anemia. However, the literature contains many examples of icterus preceding the onset of anemia. In our 2 cases the icterus was not even accompanied by anemia, and similar observations have been recorded by Astrachan,[5c] Hellman and Hertig,[12] Hoffmann and Hausmann [7] and Ross and Waugh.[6] In such instances excessive hemolysis cannot play a significant part in the production of the icterus.

Ross and Waugh, therefore, divided icterus gravis into two main groups, the hemolytic and the obstructive type. The latter term, as used by these authors, apparently refers not only to gross obstruction but to other forms of "bile stasis" and includes the possibility of a "primary dysfunction of the hepatic cells," since the van den Bergh test, on which their distinction is based, cannot be depended on to differentiate these

8. Boehncke, H.: Beitrag zur Kenntnis des Icterus gravis, Ztschr. f. Kinderh. **60**:666, 1939.

9. Ylppö, A.: Zur Klinik und Aetiologie des familiären Icterus neonatorum gravis, Ztschr. f. Kinderh. **17**:334, 1918.

10. Rich, A. R.: Pathogenesis of Forms of Jaundice, Bull. Johns Hopkins Hosp. **47**:338 (Dec.) 1930.

11. Lehndorff, H.: Anaemia neonatorum, Ergebn. d. inn. Med. u. Kinderh. **52**:611, 1937.

12. Hellman, L. M., and Hertig, A. T.: Erythroblastosis, Am. J. Obst. & Gynec. **36**:137 (July) 1938.

various forms of jaundice. The choice of the term obstructive seems unfortunate. The classic example of grossly obstructive jaundice in infancy, atresia of the bile ducts, does not give rise to the syndrome of icterus gravis. Concerning the mechanism of icterus in diffuse parenchymal disease of the liver, too little is known to justify the use of the word obstructive in such a general way. Moreover, most of the cases reported in the literature would seem to represent combination forms of the types suggested by Ross and Waugh. The distinction which they made is nevertheless useful if the more noncommittal term hepatogenous icterus is substituted for that of obstructive icterus, because it brings out the predominant role of the liver in a certain group of cases, including the 2 reported here, and may have therapeutic implications.

Possibly the clinical syndrome of icterus gravis is not etiologically homogeneous, and the "hepatic" type is a separate disease entity from the erythroblastosis foetalis group, but it is also conceivable, and indeed more likely, that the absence of anemia and hemolysis represents merely an individual variant in the response to a common etiologic agent.

The cause of hepatic damage in icterus gravis is, as yet, unknown. The much repeated opinion of earlier observers that it is due to compression of the parenchymal cells by proliferating hemopoietic cells in the sinusoids was refuted by Abt,[13] who pointed out that the same degree of overcrowding of the liver occurs in leukemia and in Niemann-Pick disease without evidence of hepatic damage. The theory would fail completely in explaining the cases in which no extramedullary hemopoiesis can be demonstrated. Other theories assume anoxic damage to the hepatic cells, anaphylaxis or a constitutional inferiority of the liver. All these explanations are as yet purely speculative, and their discussion is beyond the scope of this paper.

The derangement of the carbohydrate metabolism on the basis of impaired hepatic function in the 2 cases reported warrants special consideration. The disturbance was characterized by insulin-resistant hyperglycemia and glycosuria, sensitivity to insulin and absence of ketonuria and acidosis.

It is well recognized that diseases of the liver may be accompanied by abnormal blood sugar values or decreased dextrose tolerance.[14] The mechanism of these disturbances has been studied in detail by Conn, Newburgh, Johnston and Sheldon[15] on 6 adults with chronic hepatitis.

13. Abt, A. F.: Erythroblastosis in Icterus Gravis Neonatorum, J. Pediat. **3**:7 (July) 1933.

14. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937.

15. Conn, J. W.; Newburgh, L. H.; Johnston, M. W., and Sheldon, J. M.: Study of the Deranged Carbohydrate Metabolism in Chronic Infectious Hepatitis, Arch. Int. Med. **62**:765 (Nov.) 1938.

Normally, the liver constitutes the main organ for the regulation of carbohydrate metabolism, storing glycogen or releasing dextrose under the influence of endocrine stimuli. If either function suffers, the blood sugar level will be affected. Experimental damage or disease may inhibit the release of dextrose by the liver cells, resulting in hypoglycemia. Epinephrine cannot produce a rise in the blood sugar level in these cases, because the fault lies with the liver, which is unable to respond. On the other hand, the conversion of dextrose into glycogen by the liver cells may suffer, in which case dextrose will accumulate in the blood stream and eventually appear in the urine, the condition simulating diabetes mellitus. The fundamental difference is obvious, however. In hepatic hyperglycemia there is no insulin deficiency; consequently the oxidation of dextrose in the tissues proceeds normally. This was proved by Conn and his associates on the basis of extensive metabolic studies. The nature of the disturbance lies in the inability of the liver to act in the presence of the normally functioning stimulus of insulin to take dextrose out of the blood stream and convert it into glycogen.

The foregoing considerations are fully applicable to the 2 cases described. Both infants presented ample evidence of hepatic damage in conjunction with a deranged carbohydrate metabolism. Studies of the respiratory metabolism along the lines of Conn were not feasible, but indirect proof of the hepatic nature of the hyperglycemia is to be seen in the remarkable fact that neither child had acidosis—determination of the alkali reserve in case 1 showed no significant lowering—or produced ketone bodies in the urine. True diabetes mellitus in infants uncontrolled by insulin and complicated by infection or starvation and dehydration should produce ketonuria and acidosis. The absence of acidosis may be taken as strong presumptive evidence that the oxidation of dextrose in the tissues was unimpaired and that the apparent diabetes for which the patients were treated with insulin was in reality due to a primary inability of the liver to remove dextrose from the blood.

The impairment of the glycogenetic function of the liver is further indicated by the resistance of the hyperglycemia and glycosuria to insulin in both cases. It is to be expected that the therapeutic administration of insulin will not be effective in lowering the blood sugar when the body's own supply of insulin fails, because the liver cells are incapable of responding properly to the glycogenetic stimulus.

In view of the evidence presented, it is unlikely that either patient suffered from genuine diabetes mellitus superimposed on hepatic damage. Further proof is to be seen in the clinical manifestations. The general picture was that of hepatic disease. Instead of the classic symptoms of diabetes—polyphagia and polydipsia—there was marked anorexia in both infants. Finally, the postmortem observations must be considered.

The absence of lesions in the pancreas does not in itself exclude diabetes, since the islets of Langerhans frequently appear normal from a histologic point of view when clinically the diagnosis of diabetes is well established. Taken in conjunction, however, with the demonstration in both cases of marked lesions in the liver, with which the clinical manifestations and metabolic disturbances can be satisfactorily correlated, the negative findings in the pancreas deserve prominence as the final link in the chain of clinical evidence against diabetes and in favor of impaired hepatic glycogenesis.

The literature contains few examples of disturbance of this sort, especially in children. Bossert [2a] in 1916 observed glycosuria in a case which presented remarkable analogies to case 1 of this report. His patient had been icteric for seven weeks after birth. When the child was 11 weeks old the jaundice recurred, and at this time the child was pale, the abdomen was enlarged and the urine contained albumin and a reducing substance which was identified as dextrose by osazone and fermentation tests. At autopsy moderate ascites and an enlarged granular liver were found. Histologically the changes in the liver represented a stage of cirrhosis somewhat earlier than that of case 1. Another case in this group was included in the report of Hoffmann and Hausmann.[7] Their patient was 1 of 3 children with icterus gravis in the same family. The icterus began when the patient was 5 days old and lasted for three weeks. The child gained poorly, lacked appetite and lagged in physical growth and development. At the age of 2 years the liver was markedly enlarged, the abdominal veins were prominent and the spleen was palpable. The blood sugar was 400 mg. per hundred cubic centimeters. The urine contained reducing substances giving unstable reactions at times indicative of pentosuria. Thirty grams of dextrose given by mouth produced a definite glycosuria. The condition in the famous case of Wagner and Parnas,[16] restudied later by Helmreich and Wagner,[17] also belongs in the group of instances of hepatic glycosuria. This child had an enlarged liver and exhibited postprandial hyperglycemia and glycosuria, but on fasting there were hypoglycemia and ketonuria. The oxygen consumption following the ingestion of dextrose was normal. Epinephrine failed to cause elevation of the blood sugar level. The authors concluded that the liver was unable to assimilate and store dextrose; hence the fasting hypoglycemia (the liver stores being empty, figuratively speaking) and the postprandial hyperglycemia (the liver being unable to remove the ingested dextrose from the blood stream).

16. Wagner, R., and Parnas, J. K.: Ueber eine eigenartige Störung des Kohlenhydratstoffwechsels und ihre Beziehungen zum Diabetes mellitus, Ztschr. f. d. ges. exper. Med. **25**:361, 1921.

17. Helmreich, E., and Wagner, R.: Ueber die Phasen des Kohlehydratumbaus, Ztschr. f. d. ges. exper. Med. **45**:490, 1925.

These cases from the literature exemplify the occurrence and, to a certain extent, the mechanism of hepatogenic glycosuria in accordance with the conception of Conn and his associates. They tend to prove that the disturbance is not confined to a specific type of hepatic disease or to adult life.

The neurologic manifestations in the 2 cases reported are not necessarily of the same origin. In the younger child (case 2) the clinical picture, somnolence, weakness, flaccidity, convulsive twitchings of the face and upper extremities and periods of apnea with cyanosis, seems to be explained on the basis of the kernicterus found at autopsy. It is noteworthy, however, that the convulsions became more marked and more frequent after the administration of insulin.

In the 8 month old infant (case 1) the nature of the convulsions and of the anatomic damage to the brain is more obscure. Three possibilities may be considered: The conditions may be sequelae of a kernicterus existing during the neonatal period or reactions due to insulin or a combination of both. There is no proof that this child at one time suffered from kernicterus. There were no extrapyramidal symptoms, as in typical cases of sequelae of kernicterus.[18] The mental retardation of the patient could be explained on the basis of the mere physical handicap of a severe chronic illness in an infant and does not necessarily speak for organic damage to the brain. The presence of kernicterus in the younger brother is suggestive but not at all conclusive, for Zimmermann and Yannet[5m] have shown that only a small percentage of the cases of icterus gravis are associated with kernicterus. Moreover, the lesions in the brain were partly acute and diffuse, whereas the lesions at present considered diagnostic of the sequelae of kernicterus[19] are chronic and localized in those gray nuclei which are pigmented in the earlier phases. However, knowledge concerning the residua of kernicterus is as yet incomplete. Zimmermann and Yannet[5m] have pointed out that a certain percentage of patients anatomically proved to have kernicterus have shown no neurologic symptoms during life. Conversely, such cases as that reported by Sobel and Zucker,[2f] with a typical clinical picture but atypical diffuse cerebral lesions in a 3 year old child, suggest the possibility that the histologic changes may not always conform to the criteria now accepted. It is, therefore, impossible to exclude the presence of mild, diffuse damage to the brain due to an ancient kernicterus in this case.

Regarding the possible role of insulin, it is significant that the convulsive seizures, the first definite neurologic manifestation, appeared only

18. Fitzgerald, G. M.; Greenfield, J. G., and Kounine, B.: Neurologic Sequelae of "Kernicterus," Brain **62**:292 (Sept.) 1939.

19. Sobel and Zucker.[2f] Fitzgerald, Greenfield and Kounine.[18]

after the administration of insulin and, associated as they were with symptoms of shock, were strongly suggestive of insulin reactions. The diffuse cerebral lesions, perivascular edema, petechiae, small cystic cavities, mild focal gliosis and damage to the ganglion cells are also compatible with damage due to insulin. Similar pictures have been described in cases of hyperinsulinism reported by Baker,[20] MacKeith and Meyer [21] and others. Other observers, however, have described different changes, and there are indications that no one picture is pathognomonic. Warren,[22] therefore, stated that a purely histologic diagnosis of hyperinsulinism should not be made and required the additional evidence of a clinical history and the chemical demonstration of hypoglycemia during life. This last criterion is not present in either of our cases. The actual determination of the blood sugar during one of the seizures in case 1 showed a level of 134 mg. per hundred cubic centimeters. The explanation for the failure of insulin to produce its customary hypoglycemic effect in these cases has already been given on the basis of impaired hepatic glycogenesis.

The question arises whether insulin can produce damage to the brain without causing hypoglycemia. That the effect of insulin on the brain is not exclusively due to the hypoglycemia ordinarily following its administration has been shown by experimental studies. Popper and Jahoda [23] were able to prevent convulsions due to insulin in animals, in spite of marked hypoglycemia, by administering caffeine. Recently, Yannet [24] attempted to reverse this experiment. He first showed that large doses of insulin, while producing hypoglycemia of the same degree and duration as smaller doses, had a decidedly more toxic effect on the brain of rabbits. The author thus demonstrated the existence of a direct toxicity of insulin aside from its hypoglycemia-producing effect. However, when he eliminated the hypoglycemic effect by constant intravenous infusion of dextrose, he failed to produce convulsions or histologic changes in the brain with insulin. From these experiments it may be concluded that in the normal brain the direct toxic effect of insulin depends on the simultaneous existence of hypoglycemia. The possibility, however,

20. Baker, A. B.: Cerebral Lesions in Hypoglycemia: Some Possibilities of Irrevocable Damage from Insulin Shock, Arch. Path. **26**:765 (Oct.) 1938; Cerebral Damage in Hypoglycemia; Review, Am. J. Psychiat. **96**:109 (July) 1939.

21. MacKeith, S. A., and Meyer, A.: A Death During Insulin Treatment of Schizophrenia, with Pathological Report, J. Ment. Sc. **85**:96 (Jan.) 1939.

22. Warren, S.: The Pathology of Diabetes Mellitus, ed. 2, Philadelphia, Lea & Febiger, 1938.

23. Popper, L., and Jahoda, S.: Coffeinwirkung bei hypoglykämischen Zuständen, Klin. Wchnschr. **9**:1585 (Aug. 23) 1930.

24. Yannet, H.: Experimental Study of Pathogenesis of Cerebral Change Following Prolonged Insulin Hypoglycemia, Arch. Neurol. & Psychiat. **42**:394 (Sept.) 1939.

remains to be investigated that in a brain already damaged from other causes this separate toxic effect of insulin may produce convulsions and further damage, even if exceptional circumstances prevent the development of hypoglycemia. Such a mechanism might account for the manifestations observed in case 1; the time factor, the clinical picture and the recent anatomic lesions strongly suggest a direct toxic action of insulin on the brain. The possibility of some form of preexisting damage to the brain perhaps following kernicterus is indicated by the history and by the older lesions found in the brain. This would provide an element of increased susceptibility of the central nervous system to the direct toxic effect of insulin, which might thus have occurred, even though the hypoglycemic effect was prevented in this unusual case by the behavior of the incapacitated liver. This interpretation is, of course, entirely speculative, but it deserves mention in view of the great theoretic interest in the mechanism of damage of the brain due to insulin, and it is capable of experimental control. An absolute diagnosis is at present impossible, and the exact nature of the insulin-like reactions remains obscure.

## SUMMARY

The pathologic observations are described in 2 cases of the clinical syndrome of familial icterus gravis neonatorum associated with a derangement of the carbohydrate metabolism. Outstanding in both instances was damage to the liver. In 1 case cirrhosis had developed during an 8 month period of survival. The other patient succumbed at the end of the first week of life, with kernicterus. Severe fatty changes, hemosiderosis and deposits of bile pigment were found in the liver. No clinical or pathologic evidence of erythroblastosis was present in either case.

The predominant role of hepatic damage in these cases is emphasized in a brief discussion of the pathogenesis of icterus gravis. The question is raised whether icterus gravis without erythroblastosis forms a separate etiologic entity only superficially resembling the group of familial erythroblastoses or whether it represents merely an individual variant of a common disease process.

The unusual metabolic disturbance observed in both cases, characterized by insulin-refractory glycosuria, hyperglycemia, absence of ketosis and sensitivity to insulin, is interpreted on the basis of the pathologic findings as a manifestation of impaired hepatic glycogenesis.

After insulin therapy insulin-like reactions without associated hypoglycemia and anatomic damage to the brain were observed in 1 of the cases. The possibility of a direct toxic effect of insulin on the central nervous system in the absence of hypoglycemia is considered, and a tentative explanation is submitted.

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# LEVELS OF SULFAPYRIDINE IN BLOOD OF CHILDREN FOLLOWING DOSAGE BY BODY WEIGHT

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During the treatment with sulfapyridine of pneumonia [1] and other conditions in children we have accumulated considerable data concerning the concentration of the drug in the blood. Although we agree with Long and his associates [2] that the level in the blood is the most satisfactory guide to dosage for a given patient, we realize that it is necessary to have some program for determining the preliminary dosage for patients of various ages and sizes. Because it is simple, convenient and in accordance with accurate pharmacologic procedure, we have based this dosage on the body weight of the patient. The data presented show the concentrations of the drug in the blood that were obtained with such dosage.

## METHODS AND MATERIAL

Six hundred and fourteen determinations of the levels of free sulfapyridine were made on the blood of 126 children, averaging four and eight-tenths determinations per patient. Sixty-seven of these children received 1 grain (0.06 Gm.) of sulfapyridine per pound (0.14 Gm. per kilogram) of body weight per twenty-four hours but not over 80 grains (5.2 Gm.) per day; the remaining 59 received 1½ grains (0.09 Gm.) of sulfapyridine per pound (0.21 Gm. per kilogram) of body weight per twenty-four hours but not over 80 grains per day. All the children received an initial dose of one half of their calculated twenty-four hour dose. Sodium bicarbonate was given in amounts approximately equal to those of sulfapyridine. Dosage calculated in this manner will be referred to as the "dosage by weight."

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† Dr. Cullen died on April 11, 1940.

Merck & Co., Inc., furnished the sulfapyridine used in this study.

From the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati College of Medicine.

1. Wilson, A. T.; Spreen, A. H.; Cooper, M. L.; Stevenson, F. E.; Cullen, G. E., and Mitchell, A. G.: Sulfapyridine in the Treatment of Pneumonia in Infancy and Childhood, J. A. M. A. **112**:1435-1439 (April 15) 1939.

2. Long, P. H., and Wood, W. B., Jr.: Observations upon the Experimental and Clinical Use of Sulfapyridine: II. The Treatment of Pneumococcal Pneumonia with Sulfapyridine, Ann. Int. Med. **13**:487-512 (Sept.) 1939.

In this study all patients received sulfapyridine on the basis of dosage by weight throughout the course of medication, regardless of the level of the drug present in the blood.

For the purpose of analysis there has been made an arbitrary division of the patients into four age groups. The age distributions in each of the two dosage groups are approximately equal, as shown in table 1. The two groups are sufficiently similar in composition to warrant comparison in analysis of results. Many of the patients had pneumonia, but a variety of conditions is represented.

One hundred determinations of the levels of both free and total sulfapyridine were made on the blood of 26 of the patients. Determination of the level of free sulfapyridine only was made on the remaining 100 patients.

Sulfapyridine was dispensed in powders of many sizes (1, 1½, 2, 2½, 3, 4 and 5 grains [0.06, 0.09, 0.13, 0.16, 0.19, 0.26 and 0.32 Gm.]) for convenience in administration of the exact doses required. The calculated dose for twenty-four hours was divided into aliquot portions for administration every three hours, every four hours or, in a few instances, every six hours. The drug was suspended at the

TABLE 1.—*Data for Patients Receiving Sulfapyridine in "Dosage by Weight"*

| Age | Number of Patients | Average Weight in Pounds | Number of Determinations |
|---|---|---|---|
| Group 1: 1 Grain Per Pound Per 24 Hours | | | |
| 0-11 months | 17 | 14.6 | 64 |
| 12-23 months | 13 | 22.1 | 55 |
| 2- 4 years | 16 | 29.4 | 43 |
| Over 4 years | 21 | 47.6 | 72 |
| Group 2: 1½ Grains Per Pound Per 24 Hours | | | |
| 0-11 months | 15 | 15.8 | 107 |
| 12-23 months | 13 | 21.7 | 83 |
| 2- 4 years | 16 | 26.4 | 101 |
| Over 4 years | 15 | 45.7 | 89 |

time of administration in about half an ounce of water, and liberal consumption of fluids was urged immediately after a dose in order to promote absorption. When the drug was vomited, the same amount was given again in a half hour, and almost invariably the second dose was retained. No attempt was made to give the drug in any particular relation to meals.

Specimens of blood were drawn daily for determination of drug levels, throughout the course of medication. Marshall's method,[3] adapted for use with the Evelyn photoelectric colorimeter, was used for making the determinations. That only 0.1 cc. of blood from finger or ear was needed for this method was a distinct advantage, especially with infants.

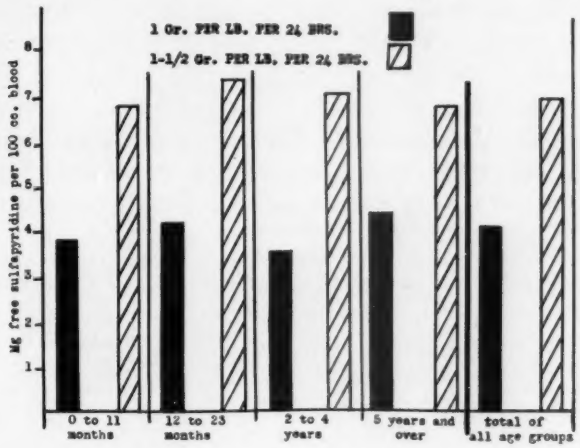
## RESULTS

As may be seen by the chart, the average level of free sulfapyridine in the blood for each of the age groups was approximately the same, and it is, therefore, apparent that age and weight were not the important factors in the variability of the levels in the blood.

The average of the several values per patient of those receiving the same dosage by weight varied rather widely from patient to patient, even

3. Marshall, E. K., Jr., and Litchfield, J. T., Jr.: Determination of Sulfanilamide, Science **88**:85-86 (July 22) 1938.

though the values corresponded closely when averaged in age groups. This variability is shown in table 2. Although the average of all patients receiving 1 grain per pound of body weight was about 4 mg. per hundred cubic centimeters, there was a variation of the average for individual patients of from 1.1 to 11.2 mg. Similarly, the patients receiving 1½


1 Gr. PER LB. PER 24 HRS.
1-1/2 Gr. PER LB. PER 24 HRS.
Mg free sulfapyridine per 100 cc. blood
0 to 11 months
12 to 23 months
2 to 4 years
5 years and over
total of all age groups

Average levels of free sulfapyridine in the blood from administration of each of the two "dosages by weight."

TABLE 2.—*Distribution of Patients by Average Value for Level of Free Sulfapyridine in the Blood*

| Average Value for Level of Free Sulfapyridine in the Blood, Mg. per 100 Cc. | Number of Patients Receiving 1 Grain per Lb. per 24 Hr. | Number of Patients Receiving 1½ Grain per Lb. per 24 Hr. |
|---|---|---|
| 1.1- 1.9 | 9 | 0 |
| 2.0- 3.9 | 27 | 9 |
| 4.0- 5.9 | 20 | 16 |
| 6.0- 7.9 | 8 | 16 |
| 8.0- 9.9 | 2 | 8 |
| 10.0-11.9 | 1 | 6 |
| 12.0-13.9 | 0 | 2 |
| 14.0-15.9 | 0 | 2 |

grains per pound, with an average of 7 mg. per hundred cubic centimeters of blood for the whole group showed a spread of from 2.1 to 15.8 mg. per hundred cubic centimeters. The range of values was greater for the group of patients receiving the larger dosage of the drug. There were 4 patients in whom the factor of receiving the upper limit of the drug (80 grains per day) came into play. These patients, who weighed 100, 57, 58 and 88 pounds (45.4, 25.9, 26.3 and 39.9 Kg.) and who received 75 or 80 grains (4.8 or 5.2 Gm.) per day, had average levels

in the blood of 2.5, 5.8, 9.2 and 5.0 mg. of free sulfapyridine per hundred cubic centimeters respectively.

Patients receiving sulfapyridine in dosage by weight showed fluctuations in the levels of free drug in the blood from day to day. The range of this fluctuation is shown in table 3, which is based on data for 86 of the patients on whom more than 3 determinations had been obtained. The results are somewhat misleading, since often a single high or low level markedly extended the range of a series of values which were otherwise fairly constant. In a general way it can be said that a certain level of free sulfapyridine was reached in the blood shortly after the onset of medication and that this level was maintained, within 2 or 3 mg., thereafter. It was noticed that the patients who received 1 grain per pound of body weight and consequently had relatively lower

TABLE 3.—*Distribution of Patients According to the Difference Between High and Low Values for Level of Free Sulfapyridine in the Blood*

| Difference Between High and Low Values for Level of Free Sulfapyridine in the Blood, Mg. per 100 Cc. | Number of Patients Receiving 1 Grain per Lb. per 24 Hr. | Number of Patients Receiving 1½ Grain per Lb. per 24 Hr. |
|---|---|---|
| 0.0- 1.9 | 7 | 2 |
| 2.0- 3.9 | 17 | 16 |
| 4.0- 5.9 | 7 | 13 |
| 6.0- 7.9 | 1 | 13 |
| 8.0- 9.9 | 1 | 3 |
| 10.0-11.9 | 1 | 2 |
| 12.0-13.9 | 0 | 1 |
| 14.0-15.9 | 0 | 0 |
| 16.0-17.9 | 0 | 2 |

levels showed less fluctuation in the levels in their blood from day to day than those who received more of the drug and had higher levels.

The level of free sulfapyridine fluctuated little from hour to hour in the course of a single day when the patient was receiving a given dosage. The results for 3 patients for whom we were able to make frequent determinations are shown in table 4. One of these had been receiving the drug for several days before the determinations recorded in the table were begun, but the others had not had the drug for some time and were started on a new course of medication with a large initial dose. It can be seen that adequate levels were reached shortly after the initial dose and that no major fluctuations resulted thereafter from the taking of medication or of meals. Of the 3 patients it can be seen also that the 2 receiving the larger dosage by weight maintained less stable levels in the blood than the 1 who received 1 grain per pound of body weight per twenty-four hours.

## COMMENT

The reason for the wide variations in the levels of free sulfapyridine in the blood among the individual children who constituted the age groups which had uniform average levels is not fully understood. It

TABLE 4.— *Variations in Level of Free Sulfapyridine in the Blood of Three Patients*

| Patient | Time | Diet | Dose of Sulfapyridine in Grains | Level of Free Sulfapyridine in Blood, Mg. per 100 Cc. |
|---|---|---|---|---|
| C. D.: Negro boy, aged 5 yr.; wt. 34 lb.; had received 48 grains of sulfapyridine per 24 hrs. (1½ grains per lb.) for 5 days preceding these determinations; this dosage was continued | Noon | Soft diet; milk 180 cc. | 6 | ... |
| | 1:00 p. m. | | .. | 2.1 |
| | 2:00 | Fruit juice 180 cc. | .. | 2.4 |
| | 3:00 | Water 180 cc. | 6 | 2.3 |
| | 3:30 | Water 180 cc. | .. | ... |
| | 4:00 | | .. | 2.3 |
| | 5:00 | Soft diet; milk 180 cc. | .. | 2.6 |
| | 6:00 | | 6 | 4.3 |
| | 7:00 | | .. | 4.0 |
| | 8:00 | Orange juice 180 cc. | .. | 3.8 |
| | 9:00 | | 6 | ... |
| | 10:00 | | .. | 2.7 |
| | Midnight | Water 180 cc. | 6 | 2.5 |
| | 3:00 a. m. | | 6 | ... |
| | 6:00 | | 6 | 2.7 |
| | 8:00 | | .. | 2.8 |
| | 8:30 | Soft diet; milk 180 cc.; water 180 cc. | .. | ... |
| | 9:00 | | 6 | 2.5 |
| | 10:00 | Milk 180 cc.; water 180 cc. | .. | 2.4 |
| | 11:00 | | .. | 2.2 |
| | Noon | Soft diet; milk 180 cc.; water 180 cc. | 6 | 2.3 |
| | 1:00 p. m. | | .. | 2.1 |
| | 2:00 | Orange juice 180 cc. | .. | 2.3 |
| | 3:00 | | 6 | 2.1 |
| | 5:30 | Soft diet; milk 180 cc.; water 180 cc. | .. | ... |
| | 6:00 | | 6 | 3.5 |
| E. L.: White boy, aged 3 yr.; wt. 25 lb.; had not received sulfapyridine for some time preceding these determinations; he was given 1½ grains per lb. per 24 hrs. | 8:00 a. m. | | 17 | ... |
| | 8:30 | Regular diet; 150 cc. fluids | .. | ... |
| | 9:00 | | .. | 1.1 |
| | 11:00 | | .. | 5.0 |
| | 11:10 | Orange juice 60 cc. | .. | ... |
| | Noon | Regular diet; fluids 150 cc. | 6 | 5.4 |
| | 1:00 p. m. | | .. | 6.1 |
| | 2:00 | Milk 120 cc. | .. | ... |
| | 3:00 | | .. | 4.5 |
| | 4:00 | | 6 | ... |
| | 5:00 | | .. | 3.6 |
| | 5:30 | Regular diet; fluids 120 cc. | .. | ... |
| | 7:00 | | .. | 5.3 |
| | 8:00 | | 6 | ... |
| | 9:00 | | .. | 6.4 |
| M. M.: White boy; aged 5 mo.; wt. 11 lb. 9 oz.; had not received sulfapyridine for some time preceding these determinations; he was given 1 grain per lb. per 24 hrs. | 6:00 a. m. | Formula 180 cc. | .. | ... |
| | 8:00 | | 6 | ... |
| | 8:45 | Fluids 40 cc. | .. | ... |
| | 9:00 | | .. | 2.2 |
| | 10:00 | Formula 165 cc. | .. | 2.8 |
| | 11:00 | | .. | 3.6 |
| | Noon | Water 180 cc. | 2 | 3.1 |
| | 12:30 p. m. | Orange juice 30 cc. | .. | ... |
| | 1:00 | | .. | 3.5 |
| | 2:00 | Formula 165 cc. | .. | 3.5 |
| | 3:00 | | .. | 3.0 |
| | 4:00 | Water 15 cc. | 2 | 3.6 |
| | 4:20 | Orange juice 30 cc.; water 65 cc. | .. | ... |
| | 5:00 | | .. | 3.5 |
| | 6:00 | | .. | 3.6 |
| | 6:30 | Formula 150 cc. | .. | ... |
| | 7:00 | | .. | 3.6 |
| | 8:00 | Water 45 cc. | 2 | 3.2 |
| | 9:00 | | .. | 3.4 |
| | 10:00 | Formula 180 cc. | .. | 3.7 |
| | Midnight | Water 15 cc. | 2 | 2.8 |
| | 4:00 a. m. | | 2 | ... |
| | 6:00 | Formula 180 cc. | .. | ... |
| | 8:00 | Fluids 65 cc. | 2 | 2.8 |
| | 10:00 | Formula 180 cc. | .. | ... |
| | Noon | | .. | 3.4 |

is probable that differences in absorption of this poorly soluble drug and differences in intake and excretion of fluid in the patients play the major roles in this variability. We have shown that age and weight can be eliminated as prominent factors in this variability if the patients are given standard dosage by weight. We have shown elsewhere [4] that conjugation of the drug into the acetylated form plays a minor part. The influence of the degree of gastric acidity and that of vomiting, diarrhea and constipation are possibly important, but they cannot be evaluated accurately at this time. Individual variation is so marked that the dosage for any given patient should be determined by the level actually present on standard dosage, with subsequent adjustment to obtain the level desired.

It is generally recognized that the therapeutically optimum level of free sulfapyridine in the blood has yet to be determined with certainty for the various types of infections in which the drug may be used. We found that a level of approximately 4 mg. per hundred cubic centimeters was therapeutically effective in the pneumonias of infancy and childhood. Consequently, since dosages designed to give higher levels are less predictable in regard to the level obtained, we recommend the "dosage by weight," with use of the smaller dosage.

## SUMMARY

A simple and convenient standard system of dosage of sulfapyridine on the basis of body weight is recommended: 1 grain per pound of body weight per twenty-four hours, with an initial dose of half the calculated twenty-four hour dose and with the total daily dose not to exceed 80 grains.

Groups of infants and children of different ages have, on the average, approximately the same levels of free sulfapyridine in the blood when they are given the same dosage according to body weight.

Individual patients receiving sulfapyridine in a dosage based on body weight show only moderate fluctuations in the levels of the drug in their blood from day to day or throughout a single day.

The averages of several individual values of patients receiving sulfapyridine in a dosage by body weight vary rather widely from patient to patient.

In view of the several types of rather marked and unpredictable variations, it must be concluded that it is desirable to make frequent determinations of the actual level present in any given patient and subsequently to adjust the dosage according to the level which is desired.

4. Wilson, A. T.; Kaely, D., and Cullen, G. E.: The Relation of Concentrations of Free to Conjugated Sulfapyridine in the Blood of Patients, Proc. Soc. Exper. Biol. & Med. **42**:187-189 (Oct.) 1939.

# URINE COLLECTOR FOR FEMALE INFANTS

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A means of collecting urine from female infants routinely without much ado would be welcomed by physicians. This device is introduced to fill the need for an efficient collector for the urine of female infants in the hospital, the office or the home. It has been tested in private practice and in several pediatric centers and found to have a remarkably high efficiency.

The collector is a unit, constructed of rubber. It has a large recess which gradually narrows to form a funnel-like spout. The recess lies next to the vulva when the device is applied. The spout protrudes about 2 inches (5 cm.) and has a standard test tube inserted into it to serve as the final resting place of the collected urine. On the inner aspect is a rubber trough, ⅛ inch (0.3 cm.) thick, which acts as a partition at the perineal area, and attached to it at its midportion is a rubber perineal button. The partition keeps the sprayed urine from dribbling into the rectum and aids it into the recess. The button and the partition also keep any feces that may be passed from working into the recess and thus prevent contamination. The collector has three flat rubber supports with safety pins at their ends for attachment to the infant's undergarment. A single support is attached anteriorly and the other two, which branch out from the perineal region, are attached to the undergarment posteriorly.

The application of the urine collector is simple, as is obvious from the accompanying illustrations. The recessed portion of the collector fits snugly over the vulva. The two perineal rubber straps are carried posteriorly and attached to the infant's undershirt. The single anterior strap is also attached to the undergarment, usually above the area of the navel. A standard test tube is inserted into the rubber spout. The urine collector now awaits the infant's action.

The advantages that this device offers are that it: (1) is a simple unit, (2) can be sterilized, (3) is easily applied by physician, nurse

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Drs. K. Blackfan, E. Brennemann, E. Park, P. Jeans, P. Aries, J. Toomey and M. L. Davis cooperated in clinical tests of the urine collector.

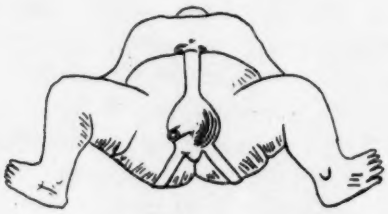

Fig. 1.—View prior to placing of the test tube in the rubber spout.

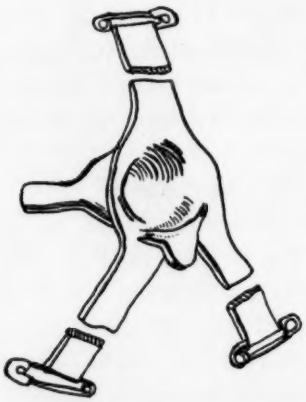

Fig. 2.—Posterior view, showing the recess, the partition combined with the perineal button and the safety pin fasteners.

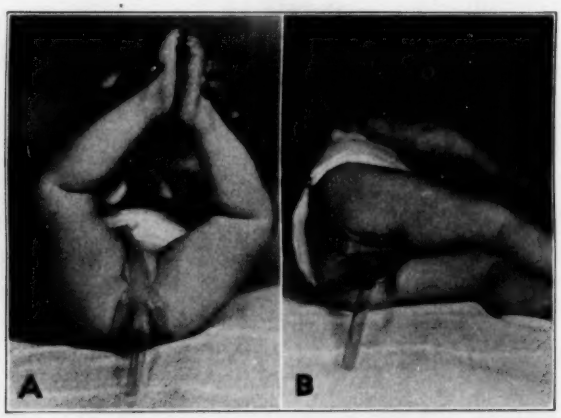


Fig. 3.—The urine collector in place. *A*, caudad view. *B*, posterior view, showing that change in position does not affect the collector.

or layman, (4) being composed of soft rubber, causes no irritation or trauma about the genitalia, (5) can be left on a considerable length of time, (6) eliminates the bother of using adhesive tape, (7) weighs less than 1 ounce (28 Gm.), (8) is remarkably efficient and (9) may be used on infant boys also, as Dr. Brennemann suggested.

## CONCLUSION

A simple, efficient, rubber collector for infant urine has been presented that will answer the demands of the physician, the nurse and the layman.

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# Case Reports

## SO-CALLED EPITUBERCULOSIS

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The term epituberculosis was originally applied to a type of chronic, nonspecific pulmonary infiltration occurring in children, which evolves on a tuberculous background, runs a protracted course and subsequently clears.[1] Although patients with this condition usually appear in good general health and exhibit little clinical evidence of illness other than low grade fever, cough and night sweats with slight loss of weight and a positive tuberculin reaction, still the massive pulmonary shadows appearing on roentgen examination of such patients led to considerable speculation over the nature, development and benign course of the pathologic process. Frequent association of these pulmonary changes with the primary tuberculous lesion found in the lungs of children left little doubt as to the important role of that lesion, but the absence of positive sputum or of tuberculosis elsewhere in the pulmonary fields and the gradual disappearance of the large shadows militated against their specificity.

Different investigators working on material from patients on whom biopsy or autopsy had been done, variously reported exudative or desquamative perifocal areas of pneumonitis about a primary tubercle,[2] serous inflammatory reactions and even healing and indurating desquamative tuberculous infiltration.[3] A few reported atelectatic areas in the involved pulmonary tissue.[4] The concept of an allergic, nonspecific reaction in previously sensitized pulmonary tissue gained considerable support. Numerous descriptive terms, such as splenopneumonia, paratuberculosis and collateral or secondary infiltration of the lung, became current and added further confusion to the use of an

From the Department of Pathology, Medical College of the State of South Carolina.

1. Eliasberg, H., and Neuland, W.: Epituberculose, Jahrb. f. Kinderh. **93**:88, 1920.

2. Zeyland, J.: Pathologische Anatomie der Lungeninfiltrierung (kollateralen Entzündung) bei Kindertuberculose, Ztschr. f. Tuberk. **68**:23, 1933.

3. Rubinstein, H.: Zur pathologischen Anatomie der Lungeninfiltrierungen, Beitr. z. Klin. d. Tuberk. **70**:773, 1928.

4. Epstein, B.: Zur Klinik der epituberculose Infiltration der kindlichen Lunge, Jahrb. f. Kinderh. **99**:59, 1922.

already loosely applied clinical definition. Of late, the carefully controlled studies of Rössle [5] have thrown more light on the nature and development of this so-called epituberculous lesion and have aided greatly in clarifying divergent opinions. Rössle emphasized the clinical observation that these massive pulmonary infiltrations do not always develop at the site of the primary tubercle in the lung and on clearing do not always leave a healed scar or a calcified focus. Further, he definitely established the fact that an epituberculous pulmonary shadow is never demonstrated unless there is tuberculosis of the bronchial lymph nodes or even glandular involvement on the same side as the primary lesion. It was proved by means of material taken at autopsy that the pulmonary shadows in the roentgenograms of patients who had previously exhibited clinical and roentgen signs consistent with epituberculosis were caused by resorption atelectasis consequent to the compression of a bronchus either by enlarged tuberculous lymph nodes or, rarely, as occurred in 1 case, by encroachment on the bronchus of the primary pulmonary tubercle itself. Thus large shadows may be produced by compression by the lymph nodes at the hilus of the lung, while smaller areas result from obstruction of narrower and more peripherally placed bronchi. Morlock and Pinchin [6] had similarly been able to demonstrate roentgenographically complete disappearance of a large shadow in the lung of a child after the bronchoscopic removal of a portion of a tuberculous hilar lymph node that was encroaching on a bronchus.

This concept of bronchial compression as a cause of the condition not only rationally explains the temporary nature of the pulmonary phenomena but tends to restrict application of the term epituberculosis to one particular variant occurring in the evolution of the initial tuberculous lesion. A brief review of some fundamental facts concerning the primary tuberculous complex, as Ranke [7] discussed them, seems helpful in clarifying later developmental possibilities secondary to involvement of the bronchial lymph nodes.

After the aspiration of tubercle bacilli into the finer ramifications of a terminal or respiratory bronchiole or into the alveoli of a previously unexposed host, the initial tubercle begins its cycle; its subsequent course is governed by the resistance inherent in the terrain in which it falls and by the number and virulence of the bacilli. The lesion usually

5. Rössle, R.: Die pathologisch-anatomischen Grundlagen der Epituberculose, Virchows Arch. f. path. Anat. **296**:1, 1935.

6. Morlock, H. V., and Pinchin, A. J. S.: Epituberculosis, Lancet **1**:1114, 1933.

7. Ranke, K. E.: Ausgewälte Schriften zur Tuberkulosepathologie, edited by W. Pagel and M. Pagel, Berlin, Julius Springer, 1928.

develops in the parts of the lung having the best ventilation, that is, the lower half of each upper lobe or the upper part of each lower lobe, a short distance beneath the pleura. In the event of high resistance of the host or of low virulence or low number of the bacilli, the early tuberculous exudate may become encapsulated, converted into scar tissue and calcified, or it may become absorbed, leaving little clue as to its original site. Greater susceptibility to the tuberculous toxins, on the other hand, causes significant alterations in the size and character of the initial lesion. Frequently the recent exudate develops into a small area of caseous pneumonia about which a specific wall of tuberculous granulation tissue forms. The overlying pleura is often involved in a perifocal reaction leading to the later formation of adhesions. With the ingrowth of fibroblasts about the caseous center, the lesion becomes spherical and is often surrounded by an outer nonspecific capsule of loose connective tissue and lymphocytes. The breaking out of crops of tubercles through the capsule may delay healing and lead to further spread of the fibrocaseous lesion, or the fibrocaseous lesion may persist as such for years. The lymphatic vessels of the lung all drain in the direction of the hilus, with the exception of those in a narrow zone beneath the pleura, and come into the field of activity early in the development of the primary lesion. Any spread of the infection is thus soon manifest in the pulmonary or bronchial lymph nodes, which are subject to essentially the same changes that occur in the pulmonary focus. The progression of the disease may stop at any one of the lymphatic barriers, and the individual lymph nodes, though linked by numerous anastomatic channels, may show great variations of response. The right lateral mediastinal lymph nodes are sometimes markedly involved in patients whose primary lesion is in the lower lobe of the left lung.[8] Rapid spread through the thoracic duct into the venous circulation may result in miliary dissemination, or equally devastating effects may be produced by purely local expansion of the lymph node lesion's causing ulceration of the bronchial wall accompanied by a discharge of caseous material into the lumen and a resulting intracanalicular spread. Likewise locally, a greatly enlarged caseating lymph node may penetrate a contiguous blood vessel or lead to the formation of an aneurysm and subsequent hemorrhage. A perifocal reaction about the node is sometimes prominent. It is only when the local progression of the tuberculous node is arrested before serious complications arise that the favorable outcome of simple bronchial compression is assured. Once healing becomes well established, regression in the size of the node permits reopening of the bronchial lumen and reaeration of the collapsed pul-

8. Jaffé, R. H.: The Pathology of Pulmonary Tuberculosis, in Goldberg, B.: Clinical Tuberculosis, Philadelphia, F. A. Davis Company, 1935, vol. 1, p. A97.

monary tissue. Only those cases in which this variation of pathologic possibilities appears fit in with the benign picture of epituberculosis.

Scarred or calcified hilar nodes appearing on roentgen examination of the chest after resolution of an atelectatic shadow in the lung bear witness to the succession of pathologic changes. The following case illustrates this point.

## REPORT OF A CASE [9]

J. R. T., a white boy of 4 years, was admitted to the Pinehaven Sanatorium for observation on July 17, 1933, because of a strongly positive tuberculin test and signs of disease in the left side of the chest. The patient was born in China in 1929, and on coming to this country in 1931 at 2 years of age he had what was believed to be lobar pneumonia of the left lung. He recovered slowly and was reported to have suffered two subsequent attacks of pneumonia on the same side prior to the present admission to the hospital. The family history was irrelevant, and there was no knowledge of definite exposure to tuberculosis. The patient's history, aside from the pulmonary involvement and pertussis, revealed nothing of importance.

*Examination on Admission.*—Physical examination on admission showed a well developed and well nourished, cooperative child not appearing acutely ill. There was diminished expansion over the left side of the chest as well as dulness over the anterior and the posterior surface over the upper half. Bronchial breathing and fine rales were noted over the same area. The apex of the heart was displaced slightly to the left. The blood pressure was 98 systolic and 64 diastolic. The urine was normal. Examination of the stool did not reveal any ova or parasites. The Wassermann reaction was negative. Examination of the blood showed: hemoglobin content, 55 per cent; red blood cells, 4,240,000; polymorphonuclears, 38 per cent; small lymphocytes, 39 per cent; large lymphocytes, 15 per cent, and monocytes, 4 per cent. A Mantoux test (1:1,000) was strongly positive. The temperature was 100 F., and the pulse rate 110.

*Course.*—A roentgenogram of the chest taken July 19 showed an area of heavy homogeneous density extending from the apex of the left lung to the lower border of the fifth rib anteriorly. The dome of the left side of the diaphragm was considerably elevated, and the intercostal spaces were somewhat narrowed. There was slight displacement of the mediastinum to the left. The bronchial markings at the hilus of the right lung were somewhat prominent, but the pulmonary fields were clear.

Fortunately roentgenograms of the chest taken on Dec. 1, 1932 (*A* in the accompanying illustration) and March 13, 1933, during the child's previous illnesses, were obtained for study and comparison. These roentgenograms showed essentially the changes noted at the examination on admission. Further inquiry into the child's history revealed that after the initial attack of pneumonia in 1931 he frequently suffered from common colds with slight fever, and that although he had been able to be up and about, numerous roentgenograms of the chest taken subsequently by different consultants showed no clearing of the pulmonary shadow.

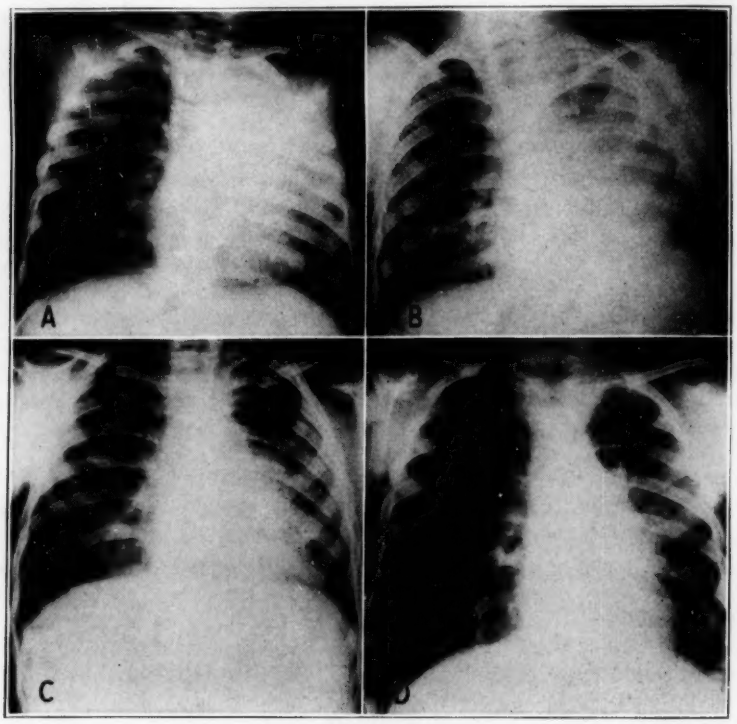
While in the hospital the patient coughed occasionally but rarely raised any sputum. A positive sputum reaction was never obtained. The temperature varied between 99 and 100 F. with sporadic excursions to 101 F. lasting for several days.

9. Dr. W. Atmar Smith placed these clinical data at my disposal.

The pulse was slightly accelerated, and the signs in the left side of the chest did not change.

A roentgenogram taken on Sept. 14, 1933, approximately two months after admission, showed the same condensation of the left lung noted in all previous roentgenograms, although there was a slight lightening beneath the first left rib anteriorly (*B* in the illustration). During this period of hospitalization, when the child was receiving supportive treatment, there was some gain in weight, and he was allowed out of bed in spite of the slight elevation of temperature.

Several roentgenograms taken during the latter months of 1933 and the early months of 1934 showed a persistence of the pulmonary shadow that had appeared




*A,* roentgenogram made on Dec. 1, 1932, showing dense infiltration of the left lung as well as elevation of the diaphragm and narrowing of the intercostal spaces. *B,* roentgenogram taken on Sept. 14, 1933, showing the slight clearing beneath the first left rib anteriorly and the persistence of the elevated dome of the diaphragm. *C,* roentgenogram made on June 12, 1934, showing the small area of density remaining beneath the second left rib anteriorly. The dome of the left side of the diaphragm has descended. *D,* roentgenogram taken on May 28, 1936, showing the persistence of a discrete area of condensation beneath the second left rib anteriorly at the site of the bronchopulmonary lymph node surrounding the left upper bronchus.

previously. In spite of this constant finding the child gained steadily in weight and never appeared particularly ill. The slight secondary anemia remained unchanged.

A roentgenogram taken on June 12, 1934, showed considerable clearing of the large shadow, there remaining only a small area of increased density close to the hilus and beneath the second rib anteriorly. The diaphragm had descended almost to its normal position (*C* in the illustration). The temperature during the latter months of hospitalization remained entirely normal. The patient was discharged on July 31, 1934, greatly improved, with a weight gain of 9 pounds (4,082 Gm.).

*Follow-Up Examinations.*—Reexamination on November 6 showed the pulmonary fields clear. A small round area of increased density was visible beneath the inner border of the second left rib and had the appearance of a partially calcified bronchopulmonary lymph node. There was a small adhesion on the dome of the left side of the diaphragm, but the position of the diaphragm was normal.

The child remained entirely well. Repeated roentgenograms of the chest taken on June 25, 1935, and May 28, 1936, displayed persistence of the lymph node shadow previously seen (*D* in the illustration). The last roentgenogram, made on June 4, 1939, showed no significant changes.

## COMMENT

The duration of this massive pulmonary shadow, lasting for three years, followed by complete resolution and the appearance of a dense circumscribed area in the region of the left bronchopulmonary lymph nodes, points significantly to previous bronchial compression in the region of the bronchus of the upper lobe of the left lung. Characteristic of atelectasis were the elevation of the diaphragm on the affected side, the narrowing of the intercostal spaces and the slight shift of the mediastinum. The age of the patient, the positive tuberculin reaction and the clinical well-being out of proportion to the pulmonary signs are also in keeping with the complex of primary tuberculosis of the lymph nodes. The primary pulmonary lesion itself is not demonstrable in the later roentgenograms of the lungs, but, as previously noted, this lesion may be minimal even in the presence of considerable involvement of the lymph nodes. It is possible that the primary tubercle occurred in the lower lobe of the left lung at the site of the adhesion noted on the roentgenograms. While in this case there was a constant pulmonary shadow of long duration, it seems likely that transient clearing could be repeatedly produced by a temporary regression in the size of the tuberculous nodes compressing a bronchus, permitting reestablishment of the continuity of the lumen. Such endoglandular regressions and exacerbations might also account for the reappearance of dense pulmonary shadows after the administration of tuberculin some time after clearing has taken place, as reported by Langer [10] and by Goldberg and Gasul.[11]

10. Langer, H.: Die Spezifität rückbildungsfähiger Lungeninfiltrate bei kindlichen Tuberculose, Ztschr. f. Kinderh. **34**:142, 1922.

11. Goldberg, B., and Gasul, B. M.: Epituberculosis, Am. J. M. Sc. **180**:824, 1930.

The relative infrequency of this clinical picture among adults is compatible with the rarity of the primary lymph node complex in adults. However, in the case of an endoglandular exacerbation occurring in later life, the ability of an involved node to become large enough to cause compression of a bronchus may be somewhat limited by old scarring within the node as well as by increased rigidity of the bronchial wall. As epituberculosis appears to represent a single phase or variant of the numerous pathologic changes possible during primary tuberculosis of the lymph nodes, it seems advisable to restrict the term to apply only to cases in which roentgenographic evidence of resorption atelectasis is followed by complete resolution and clinical recovery.

SUMMARY

The epituberculous lesion occurring in children is constantly associated with the complex of primary tuberculosis of the lymph nodes.

The massive pulmonary shadows noted on roentgen examination appear to be caused by resorption atelectasis consequent on compression of the bronchus by enlarged tuberculous lymph nodes.

A case in which a large area of pulmonary atelectasis persisted for three years in a child who exhibited only mild clinical symptoms and a strongly positive tuberculin reaction is reported. On clearing of the pulmonary field, prominent lymph node shadows were demonstrable at the hilus of the involved area.

Various pathologic changes may result from involvement of the bronchial lymph nodes in the primary tuberculous lesion, and it is suggested that the term epituberculosis be confined to those cases in which pulmonary atelectasis resulting from bronchial compression is followed by resolution and clinical recovery.

# POLYCYTHAEMIA VERA IN CHILDHOOD

## REPORT OF A CASE WITH CHANGES IN THE SKULL

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AND
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In late years attention has been drawn to the thickenings of the skull in some diseases of the blood among children. These have been repeatedly described both in the disease of Cooley, the erythroblastic anemia of the Mediterranean nations, and in the peculiar sickle cell anemia which is largely confined to American Negroes. Changes in the skull are also noted sometimes in ordinary hemolytic anemia. In this article we want to show that there exists still a fourth disease of the blood among children in which a similar thickening of the skull is possible, viz., polycythaemia vera, or Vaquez' disease. Of this, however, we have observed only 1 case. This is not to be wondered at with so rare a disease, of which there are among children hardly a dozen cases known, in only 1 of which was autopsy performed. The case reported here concerns a boy whom one of us described in 1932.[1] We were able to follow this child regularly from then till he died in 1938 at the age of 12. In 1936 this patient was described once more in consequence of a then instituted therapy with an arsenic preparation.[2] We are of the opinion that we should once more present this case, not only because the sequel and the conclusion of so rare a disease may be of importance but also because a careful autopsy was performed.

### REPORT OF CASE

Jan P., the patient (fig. 1), besides polycythemia showed some congenital anomalies, viz., tower head, hypospadias and curved little fingers typical of mongolian idiocy. He was a bright child, playing the whole day in the street with his friends without tiring. The only complaint was headache, especially in hot weather. Further, the boy was thin, and he showed the flushed color peculiar

From St. Elizabeth's Hospital.

1. Halbertsma, T.: Polycythemia in Childhood: Report of Case in Boy, Six Years Old, with Tower Head, Am. J. Dis. Child. **46**:1356 (Dec.) 1933.

2. Halbertsma, T.: Un cas de polycytémie véritable traité par l'arsenic à fortes doses, Rev. franç. de pédiat. **12**:120, 1936.

to the disease which had procured for him the nickname of "the Indian." His eyes often appeared bloodshot from the many dilated blood vessels in the sclerotics; also on the trunk he showed numerous engorgements of the veins. The spleen was greatly enlarged and firm and appeared more than a half hand breadth below the arcus costarum; the liver was not enlarged but felt firmer than normal. The blood picture was typical of Vaquez' disease. The hemoglobin percentage was from 130 to 140 (Sahli); the number of chromocytes varied between 8,500,000 and 11,500,000; the number of leukocytes was normal, but a high percentage (about 8 per cent) of eosinophilic cells was always found. The total quantity of blood was greatly increased and amounted to about 3 liters. The sedimentation rate of the blood was hardly measurable and amounted, after twenty-four hours, to 2 or 3 mm. at most. The heart was not enlarged on percussion. Sometimes a

Fig. 1.—Jan P., aged 6 years (1932), showing tower head.

systolic murmur was to be heard. One day this would be perceptible but the next day it would have disappeared again. In view of these symptoms we had to find out if we were dealing with a case of polycythaemia vera or of morbus caeruleus. In the latter disease an important cardiac defect should exist with a secondary compensatory polycythemia. We are now of the opinion that in the first article on this patient evidence of polycythaemia vera was given. Arguments for polycythemia were: the great vitality of the child, who was never tired or short of breath; the red, not blue, complexion; the large increase in the number of red blood corpuscles, higher than is the rule with morbus caeruleus; the absence of clubbed fingers; the enlargement of the spleen without enlargement of the liver; the normal roentgenogram of the heart, which was small rather than large; the normal electrocardiogram; the increase of the total blood volume, and, finally, the normal diameter of the chromocytes. The good general condition militated

against tuberculosis of the spleen as the possible cause of polycythemia. All these facts led us to believe that our patient must indeed belong to the small group of children with polycythaemia vera.

After having tried without success a therapy consisting of venipuncture and administration of splenic preparations, and having rejected as too dangerous other therapeutic methods, such as treatment with benzene or phenylhydrazine and irradiation of the long tubular bones with radium or roentgen rays, we proceeded to use an arsenic preparation in large quantities, as described by Forkner, Scott and Wu[3] for adults. Though at first it must cause some surprise that in larger doses the ancient remedy against anemia, arsenic, might have an opposite effect in polycythemia, confidence should be put in the well documented description of the success with 6 patients, 5 of whom improved a great deal. The results with our patient proved that our American colleagues were right, for under a therapy with about 1 cc. of a solution of potassium arsenite a day, a decrease in the number of chromocytes and in the hemoglobin percentage and diminution of the headache and the intensity of the red complexion were observed. The success of therapy, though constant, was not complete; we could reduce the number of chromocytes from 8,500,000 to 11,500,000 to about 7,000,000 and once even to below 6,000,000 but not more. If we gave large quantities of the arsenic preparation, slight symptoms of poisoning set in: lack of appetite, weariness and diarrhea. In this event the therapy was stopped or continued with half quantities. Once the blood showed polychromasia, anisocytosis, a trace of poikilocytosis and a basophilic stippling of the chromocytes, as in lead poisoning. When treatment was stopped the number of cells began to climb to the old level again after some weeks. Our impression of this treatment was that though it did not effect a cure it nevertheless enabled us to make the most annoying symptoms, such as headache, disappear. In a certain way we could restrict the disease with it, for we could make the number of chromocytes decrease 2,000,000 or 3,000,000 per cubic millimeter; there were no disadvantages worth mentioning to this method of procedure. However, after some lapse of time the regular use of the arsenic compound gave rise to an objectionable symptom. In June 1936 it struck us that the child's skin had a peculiar color, viz., a gray ground color with subtle white dots, especially on the trunk. It was clear that this was a form of arsenical melanosis which is known as leukomelanoderma; the white spots must be considered as points where the melanotic process was absent. The back of the child's hands showed a more equal distribution of melanosis, whereas on the palms and soles a distinct hyperkeratosis could be seen. Because of the probability that a considerable arsenic depot had been formed in the patient, the administration of solution of potassium arsenite was stopped for some time. After four months the number of chromocytes began to rise again to the old height of about 9,000,000 and the greater part of the discoloration of the skin disappeared.

In March 1937 the patient again came under clinical observation for albuminuria. He had gradually grown into a fairly tall boy of 11 years, and it struck us that his head had not only become higher but broader in the course of years. Unfortunately no photograph was taken at this time; neither did we take new roentgenograms. The albuminuria appeared to be rather considerable; 0.5 to 0.75 per cent of albumin was excreted in the urine, which contained only a few formative

3. Forkner, C. E.; Scott, T. F. M., and Wu, S. C.: Treatment of Polycythemia Vera (Erythremia) with a Solution of Potassium Arsenite, Arch. Int. Med. **51**:616 (April) 1933.

elements, a few leukocytes and occasionally a chromocyte but never cylinders. The temperature was not raised; at the apex of the heart we found a murmur. The urea and the sodium chloride percentages of the blood were normal; therefore, the picture made us think of nephrosis though edema was absent. It was, however, impracticable for us to make an albumin spectrum of the blood in the usual way to support this diagnosis, because it was not possible to separate the blood serum by centrifugation. With an extremely strong centrifuge, nevertheless, the chemist of the Leyden Pediatric Clinic, J. van Ormondt, succeeded after many hours' turning in pipetting from 100 cc. of blood a single cubic centimeter of serum, after which he contrived to fix, with the spreading method of Gorter, an albumin percentage of 5.7 and a globulin percentage of 4.4. These figures were not evidence in favor of the diagnosis of nephrosis, and we could not institute a definite course of therapy. The patient went home after five weeks, not cured and without a definite diagnosis. He was not given any more of the arsenic compound. In November 1937 he suffered from chorea minor; this disease was rapidly cured. Albuminuria still existed (up to 5 per cent).

Death occurred in February 1938. The child was brought to us in an unconscious condition. A fortnight before an abscess had developed on the neck, at first without a rise of temperature. But on the day before admission he became drooping and feverish and grasped at his head; he had incontinence and soon lost consciousness. On examination we found a comatose, restless, moaning child with marked stiffness of the neck, high reflexes, a positive Babinski sign and dilated pupils. The temperature rose to 40.2 C. (104.3 F.). At the side of the neck an abscess as big as a hen's egg was found, which both to us and to the surgeon looked like a cold abscess. The heart beat rapidly but was otherwise normal. The tone of the lungs on percussion was slightly tympanitic. The general impression was that of a patient with meningitis; the probability that the lesion on the neck was a cold abscess and the positive reaction to the Pirquet test, known to us before, made tuberculous meningitis seem most likely. Our surmise was strengthened by the roentgenogram of the lungs (fig. 2), on which we observed numerous blotches which reminded us of tuberculous areas. This opinion was supported by the report of the oculist, who stated that there was on both sides retinitis and papillitis tuberculosa. Apparent confirmation was given by spinal puncture, which produced a somewhat opalescent liquid containing 300 cells per cubic centimeter but no micro-organisms, but which reacted positively to the Nonne and Pandy tests. To our surprise, however, the expected increase of pressure was absent; only 15 cc. of water pressure was measured. There was not much time for further investigations, for the child sank rapidly; the respiration became slow and deep, the pulse extremely frequent. Without having recovered consciousness, he died after two days. Our diagnosis was polycythaemia vera with meningitis of a probably tuberculous nature.

*Autopsy.*—One change was exceedingly striking, i. e., the marked hyperemia. Every organ was hyperemic; from every vessel that was severed an unknown quantity of blood streamed forth; in every serous membrane and in the skin were subtle networks of dilated vessels, filled with blood.

The cause of death appeared to be septicemia. We thought it likely that this had originated in the abscess under the right side of the lower jaw. Here we found not a tuberculous abscess but one with a phlegmonous inflammation around it caused by streptococci. Extensive fresh endocarditis verrucosa of the mitral valves was found. On microscopic examination these verrucae proved to be laden with streptococci. We found acute inflammation not only of the mitral valves but

of one of the chordae tendineae, which was much thickened; this can have resulted only from a much older inflammation. It should be pointed out that this lesion was so limited that a valvular defect cannot have existed. The heart was not enlarged; it weighed 160 Gm. No other changes were found in the heart, except many coccic emboli in the capillaries of the muscle. These we also found in the capillaries of the spleen. Streptococci were cultivated from the mitral valves and the pulp of the spleen.

Meningitis was found, which should likewise be considered a result of septicemia. From the cerebrospinal fluid, drawn post mortem, streptococci were grown; a guinea pig into which this fluid was injected did not show any tuberculous lesion after three months. The leptomeninges were so hyperemic that macroscopically no exudate was seen. On microscopic examination, only meningitis was found.

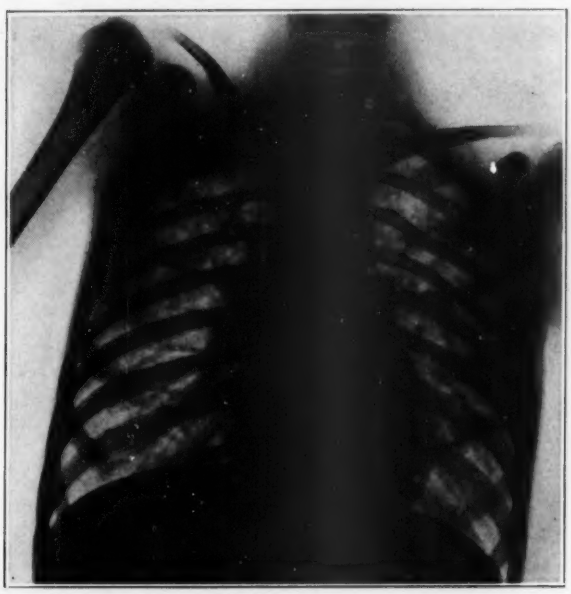

Fig. 2.—Roentgenogram of the thorax one day before death, showing multiple foci, apparently tuberculous, which were caused by marked hyperemia.

The bone marrow showed such hyperplasia that nowhere, neither in the skull, the sternum, the femur, the ribs nor in the spinal column, did we see any fat cells. All bone meshes were filled with marrow rich in cells and blood, and the marrow of the femur had large cavities filled with blood. In no other organ was the hyperemia so marked as in this tissue. The subtler structure of the marrow did not show striking changes. There were fairly many normoblasts. The number of megakaryocytes seemed normal to us; there was some segmentation of the nuclei.

In the greatly enlarged spleen, which weighed 500 Gm., there was an enormous hyperplasia of the so-called red pulp, which explained its enlargement. Only a little ferruginous pigment was found in it. Neither the spleen nor the hemolymph glands showed any evidence of a fresh formation of blood. There was no evidence of tuberculosis in either the spleen or the lungs. There were no adhesions between

the lungs and the chest wall. The lungs were from their very nature hyperemic; they retained the air well. The blotches found on the last roentgenogram can be ascribed only to localized overfilling with blood. Examination of the larynx, trachea and esophagus yielded nothing special. The liver was the size of that of an adult. On microscopic examination only hyperemia was found. The kidneys were of normal size. In the right kidney ischemic necrosis was found, which can be easily explained by the acute endocarditis. There was no degeneration of the renal epithelium. The pelves of the kidneys, the ureters and the bladder were normal, except for hyperemia. The testes were not descended; the testicular tissue was normal, however. No explanation for the albuminuria in the last year of life was found; nephrosis may be excluded. The aorta had a smooth intima.

Fig. 3.—Inside view of thickened skull in polycythaemia vera.

Elsewhere the organs were normal except for hyperemia. The hypophysis, thyroid, parathyroids and the adrenals, as well as the tissue of the brain, were hyperemic.

The skull cap, breast bone, some ribs, some vertebral bodies and the left thigh bone were examined. In the last four bones no striking changes were found. It is possible that the bone tissue in these parts of the skeleton had increased somewhat more than is normal in the course of polycythemia, but this increase was so slight that on comparison with the same bones of a girl of 15 (dying from rheumatism) we could determine no definite change, even though we were of the opinion that the ribs were abnormally hard on section.

The skull cap was considerably thickened, especially in the frontal bone, but the base of the skull was not thickened and the sella turcica was not enlarged. Further, the sutures of the skull cap were closed. On the inside it was seen that the grooves in which the arteriae meningeae had run were strikingly deep (fig. 3).

The three plates of which a normal skull cap consists—tabula externa, diploe and tabula interna—were missing; this skull cap seemed to be built up from one

thick homogeneous layer of bone. Microscopic examination confirmed this. The cap consisted of a close fabric of spicules of bone; perhaps it is better to speak of bony partitions between which the marrow rich in cells lay. The tabula externa was missing; no close bony plate was formed on the outside. Here something of

Fig. 4.—*A*, frontal cross section of skull in polycythaemia vera (top) and similar section of the normal skull of a 15 year old girl. *B*, magnification of sections in *A*, showing absence of the tabula externa in the thickened skull; × 3.

new formation of bone might be seen in the shape of spicules of plexiform bone. On the interior a closing bony plate, though thin, was found. This may be considered as the tabula interna. This was confirmed by microscopic examination.

The skull was sawed through in the frontal plane, and a slice was macerated in a strongly alkaline solution of sodium hypochlorite. The result is shown in figure 4, in which this slice has been photographed beside a similar slice from the skull of a girl of 15. Not only the difference in thickness is striking but the differences in structure, there being absence of the tabula externa and increase of the diploe, whereas the tabula interna is only slightly indicated. The thickening of the skull thus rests on an increase of the diploe.

### COMMENT

At autopsy the complete picture of the original disease, polycythemia, was found as it is known in the adult. There existed general hyperemia of all organs, a markedly enlarged spleen and an extremely active red bone marrow. But besides there was as an important new symptom, the thickening of the skull. The question arises whether the thickening of the skull bears any connection with the polycythemia. In the literature we found only 1 case of polycythemia in a child (that of Hottinger [4]) which includes an autopsy report. This concerned a child aged 6 years who died of a complication after two years; on postmortem examination gross tuberculous lesions were evident. Through cachexia the symptoms of polycythemia had been greatly reduced, yet this diagnosis could still be confirmed. The skull cap of this child was described as follows: front, narrow; back, broader; more than moderately thick with ample hyperemic diploe.

A case of general osteosclerosis in an adult with polycythemia has also become known (Hirsch [5]), but in that case only the vertebrae, ribs and femur were examined. In view of this the connection between the changes of the skull and the polycythemia seemed to us doubtful as yet. The only point of contact with our patient who had a tower head seemed to us the well known observation of Gänsslen,[6] who has described the appearance of tower head in another disease of the blood, hemolytic anemia. It has, however, appeared that the percentage of tower heads in his series of cases accidentally turned out to be fairly high, for others could not confirm his observations. Debré [7] in 25 cases found a tower head only 4 times. No roentgenographic or anatomic examinations were made in the cases of Gänsslen. There are, however, two reports of changes in the skull in hemolytic anemia similar to ours. In the first place, Snelling and Brown [8] found in a girl of 6

4. Hottinger, A.: Beiträge zur Kenntnis der kindlichen Polycythämie, Ztschr. f. Kinderh. **44**:61, 1927.

5. Hirsch, E. F.: Generalized Osteosclerosis with Chronic Polycythemia Vera, Arch. Path. **19**:91 (Jan.) 1935.

6. Gänsslen, M.: Die hämolytische Konstitution: Klinische Fortbildung, in Klemperer, G., and Klemperer, F.: Neue deutsche Klinik, 1936, Berlin, Urban & Schwarzenberg, vol. 4 (supp.).

7. Debré, R.; Lamy, M.; Sée, G., and Schrameck, G.: Congenital and Familial Hemolytic Disease in Children, Am. J. Dis. Child. **56**:1189 (Dec.) 1938.

8. Snelling, C. E., and Brown, A.: Case of Hemolytic Jaundice with Bone Changes, J. Pediat. **8**:330, 1936.

a skull which was not thickened and in which the tabula externa was missing. The diploe constituted, with radiary offshoots, the exterior of the skull. As the disease greatly improved after extirpation of the spleen, only a roentgenographic examination of the skull was performed. Secondly, Debré mentioned that in 1 of his patients a thickening of the skull cap was visible on the roentgenogram and at the same time the radiary streak was to be found on the outside. Similar skulls with radial offshoots on the roentgenogram, which are also found in the erythroblastic and sickle cell anemias, are called by Americans "hair on end skulls," by the French, *crâne en brosse.* It is possible that a roentgenogram of the skull of our patient with polycythemia, taken shortly before death, would have shown the same design.

More important, therefore, are the changes in the skull which are found in anemia erythroblastica (Cooley's disease). This disease is a hemolytic anemia which Cooley first described in America in children whose parents originated from Italy, Greece and Syria, in short, from the Mediterranean region. Later this disease was found in those countries and also in the south of France. This disease is familial and has a bad prognosis. In numerous cases thickenings of the skull have been observed and also anatomically examined. The pictures which are found in the articles published by Koch and Shapiro [9] and by Whipple and Bradford [10] show a striking likeness to the skull cap seen in our case of polycythemia. Here, too, the thickening is the result of an increase of the diploe; on the picture in the last-mentioned article it is clearly visible that the tabula externa is missing while the tabula interna is thin (fig. 5).

There exists still a third kind of hemolytic anemia in which changes of the skull cap are found. This is sickle cell anemia, a disease repeatedly described among Negro children in the United States. In this disease thickening of the skull occurs which on the roentgenogram shows a great likeness to that in anaemia erythroblastica with absence of the tabula externa and thickening of the diploe. We have nowhere found an anatomic description. For the present we must content ourselves with the roentgenographic pictures which are among others found in the article of Grinnan.[11]

In these three anemias a hyperplasia of the bone marrow is found. This occurs especially in anaemia erythroblastica and in sickle cell

9. Koch, L. A., and Shapiro, B.: Erythroblastic Anemia: Review of Cases Reported Showing Roentgenographic Changes in Bones and Five Additional Cases, Am. J. Dis. Child. **44**:318 (Aug.) 1932.

10. Whipple, G. H., and Bradford, W. L.: Racial or Familial Anemia of Children Associated with Fundamental Disturbances of Bone and Pigment Metabolism (Cooley-Van Jaksch), Am. J. Dis. Child. **44**:336 (Aug.) 1932.

11. Grinnan, A. G.: Roentgenologic Bone Changes in Sickle Cell and Erythroblastic Anemia: Report of Nine Cases, Am. J. Roentgenol. **34**:297, 1935.

anemia to a strong degree. There exist important points of agreement between these three hemolytic anemias on one side and polycythemia on the other side. These are: (1) thickenings of the skull which greatly resemble one another—absence of the tabula externa and increase of the diploe; (2) hyperplasia of the bone marrow, and (3) occurrence in children. On the basis of these points of agreement we assume a connection in our case of polycythemia between the disease of the blood and the thickening of the skull, a connection which is generally accepted in the aforementioned anemias. We do not consider the change in the skull in polycythemia as a curiosity in itself but as a change which is found in a series of diseases of the blood.

An explanation of this thickening of the skull is as yet difficult to give. With all these diseases there exists, however, hyperplasia of the bone marrow; it is imaginable that through this in the growing individual the change in the structure of the skull comes about, coinciding with hypertrophy of the bone tissue. It is, however, not understood why there is an absence of hypertrophy of the bone tissue in the other bones.

Fig. 5.—Thickening of the skull in erythroblastic anemia (from Whipple and Bradford [10]).

## SUMMARY

A child with polycythaemia vera and tower head died, at the age of 12, of an intercurrent disease after an observation period of seven years. At autopsy a marked thickening of the skull cap was found. On a roentgenogram taken six years before hardly anything of this was perceptible. This thickening of the skull also occurs in the erythroblastic anemia of Cooley, in sickle cell anemia and sometimes in ordinary hemolytic anemia. A connection between the disease of the blood and the change in the skull may be assumed in polycythemia as well as in the three mentioned anemias.

# PROJECTILE VOMITING AND INTOXICATION IN THE NEWBORN INFANT

## REPORT OF TWO CASES DUE TO CONGENITAL STRICTURES OF THE URINARY TRACT

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BROOKLYN

Forceful and excessive vomiting is frequently encountered in infants during the neonatal period and is usually due to some disturbance related to the gastrointestinal tract. It may arise from disturbances other than those of the gastrointestinal tract, such as intracranial trauma, which has received considerable emphasis. However, gastrointestinal symptoms in the newborn due to obstructive lesions of the genitourinary system have received almost no mention in the pediatric literature. Recently, I observed 2 infants who exhibited symptoms of anorexia, projectile vomiting, drowsiness and progressive and generalized edema. These babies were dramatically ill and seemed to be in danger. In each case the vomiting was so persistent and excessive that roentgenographic studies were made of the gastrointestinal tract. Surprisingly, instead of evidence of pathologic gastrointestinal conditions, marked distention of the urinary bladder was revealed. The distention was caused in each case by a stricture of the urethral opening. Dilatation of the meatus relieved the distention of the bladder, and in each case the symptoms promptly and completely subsided. Because I have encountered these 2 similar cases, I believe that others may occur and might easily be overlooked. For this reason the course of each infant has been recorded in detail.

### REPORT OF CASES

CASE 1.—L. B., a male infant, was born at term by cesarean section, weighing 3,460 Gm. (7 pounds 9 ounces). The pregnancy was normal. Physical examination at birth revealed a vigorous, normal infant. On the second day of life a formula consisting of diluted cow's milk with 5 per cent added carbohydrate was taken readily, and all but one of the feedings were retained. However, on the third day the formula was not well taken, and three of the feedings were forcefully vomited. Human milk was substituted for the cow's milk formula. On the fourth and fifth days of life, the baby was listless and drowsy and refused to nurse. When forcibly fed, the infant immediately vomited. There were considerable amounts of bile. Except for the marked drowsiness previously noted, there were

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no abnormal findings. The child was reported to have voided frequently. The stools were of normal frequency and appearance. No peristalsis or intestinal patterns were observed.

Because of the listlessness, a hypodermoclysis consisting of 80 cc. of physiologic solution of sodium chloride was given, and 30 cc. of paternal blood was administered intramuscularly. Atropine sulfate ($\frac{1}{1.000}$ grain [0.00006 Gm.]) was given before each feeding. A urinalysis and a blood count on the fourth day revealed no abnormal findings. On the fifth, sixth and seventh days of life the drowsiness continued, and the projectile vomiting occurred with every feeding. The weight, which had previously decreased, showed increase on the seventh day, although little if any food had been retained. Slight edema of the dorsum of the hands and feet was observed at this time.

Because of the extreme inability of the infant to retain food, the possibility was entertained that some anomaly of the upper part of the gastrointestinal tract

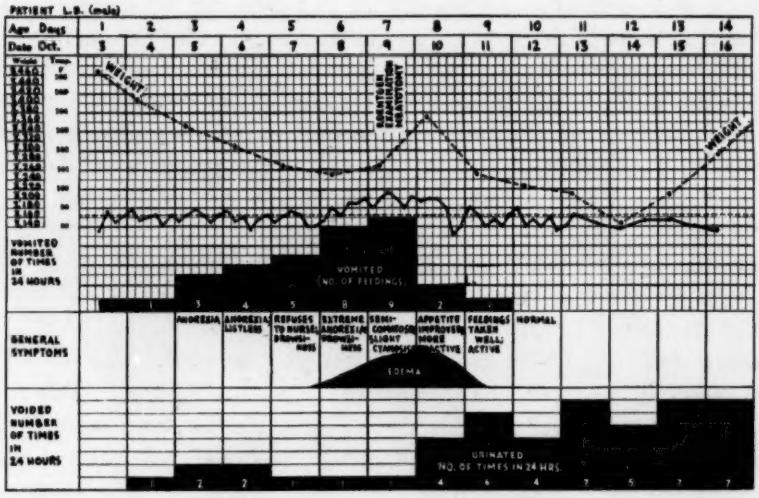


Fig. 1 (case 1).—Graphic representation of the symptoms and clinical course before and after meatotomy and catheterization.

existed. Furthermore, because of the presence of bile in the vomitus and some milk curds in the stools, it was felt that the most likely diagnosis was partial duodenal obstruction. Roentgenographic examination of the gastrointestinal tract was requested.

A film of the entire body in the anteroposterior position was made prior to the administration of barium sulfate by mouth. This film (fig. 2*A*) was interpreted (by Dr. A. L. L. Bell) as follows: "Thoracic cage and contents appear normal. The abdomen reveals normal gas distribution. The liver and splenic shadows appear normal. The urinary bladder seems definitely distended. Inquiry revealed that the child had not urinated for at least three hours. Immediately after this film was exposed, however, the baby did urinate, and on reexamination the bladder remained dilated. Conclusion: Some type of obstruction of the lower part of the urinary tract. Would suggest clinical investigation of this site before proceeding with the gastrointestinal examination."

Within a few minutes after the roentgenologic diagnosis of obstruction of the lower part of the urinary tract, an attempt was made to insert a no. 10 F. soft rubber catheter into the bladder. The redundant and adherent foreskin was partially freed from the glans, and a small pinpoint-sized meatus was seen. Meatotomy was performed, and the child immediately voided, the stream being forceful and of normal size. The catheter was then passed easily to the bladder, but 3 cc. of residual urine being obtained. A roentgenogram was made immediately and revealed absence of the shadow previously cast by the urinary bladder (fig. 2 *B*).

After the meatotomy, the infant voided unusually large amounts of urine at frequent intervals. Within eight hours it was noted that the child was more alert, was eager for food and had entirely stopped vomiting. Within eighteen hours the edema had disappeared, and the infant appeared and acted normal in every way. The subsequent course was uneventful.

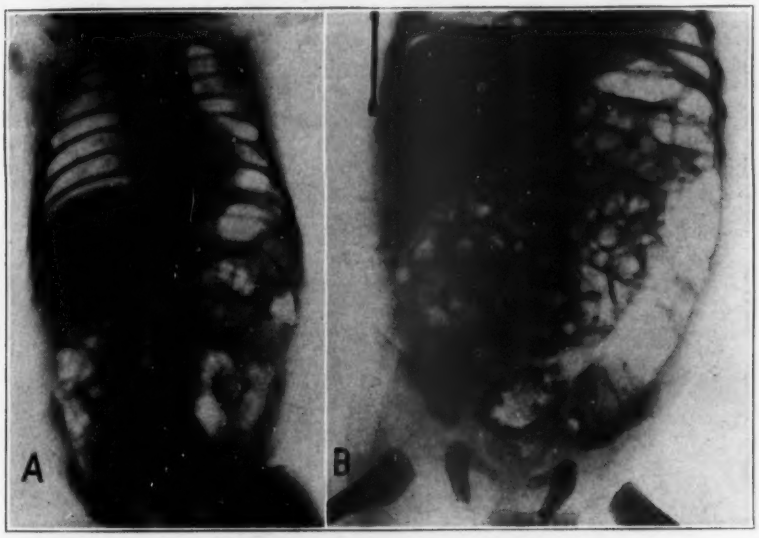


Fig. 2 (case 1).—*A*, ordinary roentgenogram showing the markedly distended urinary bladder. *B*, roentgenogram taken after meatotomy and catheterization. Note the absence of the shadow previously cast by the bladder.

Case 2.—E. R., a female infant weighing 2,740 Gm. (6 pounds) was delivered by low forceps. Physical examination performed eight hours after birth revealed no apparent abnormality. No unusual occurrences were noted until the second day, when it was observed that the child was listless and did not care to take water or to nurse at the breast. On the third day it was so difficult to awaken her that forceful stimulation was required to elicit crying. The breast was refused, so that artificial feeding was substituted. When the feedings were forcibly administered, they were promptly vomited. Reexamination revealed a markedly apathetic, listless child without evident physical conditions to explain the symptoms. Although the infant appeared well hydrated, a hypodermoclysis consisting of 80 cc. of physiologic solution of sodium chloride was administered.

This unfavorable situation, with listlessness, anorexia and projectile vomiting, continued until the fourth day. A gain in weight was recorded, although prac-

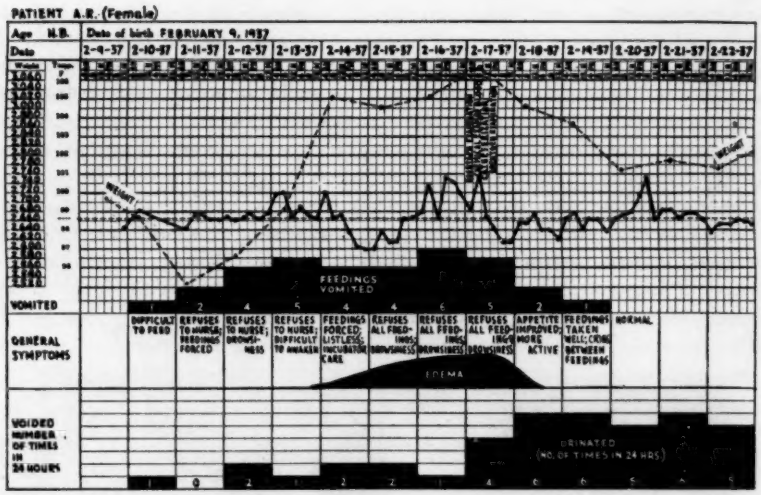


Fig. 3 (case 2).—Graphic representation of the symptoms and clinical course before and after dilation of the meatus and catheterization.

Fig. 4 (case 2).—Roentgenogram made after dilation of the meatus and catheterization. Note the absence of upward displacement of the intestines.

tically no food had been retained. Reexamination still revealed no apparent cause for the drowsiness and vomiting. Atropine sulfate (1/1,000 grain [0.00006 Gm.]) was given before each feeding. Urinalysis and blood count revealed normal conditions. On the fifth day the weight again increased, although no food had been retained. Edema of the feet, legs and hands was noted at this time. For three days more the vomiting continued, and roentgenographic studies of the gastrointestinal tract were begun on the eighth day. The barium was well retained, and a film exposed two hours later revealed no evidence of pathologic change in the gastrointestinal tract other than moderate hypomotility. However, it was noted that the barium-filled intestines were displaced upward from the pelvis, probably by a distended urinary bladder. A diagnosis of obstruction of the lower part of the urinary tract was suggested. Before urethral catheterization was attempted, venipuncture was performed, and blood was withdrawn for chemical studies of its composition. The results were: dextrose, 81 mg. per hundred cubic centimeters; nonprotein nitrogen, 24 mg.; urea, 19.5 mg.; urea nitrogen, 9.1 mg.; uric acid, 2.5 mg.; creatinine, 0.88 mg.; sodium chloride, 591 mg.; serum phosphorus, 5.8 mg.; serum calcium, 10.1 mg.; total serum protein, 5.60 Gm.; albumin, 3.66 Gm.; globulin, 1.94 Gm.; cholesterol, 156 mg. The icterus index was 8.5. These findings were considered normal for a newborn infant, except possibly that the serum protein level was slightly decreased.

Attempts to insert a no. 12 F. soft rubber catheter into the urethra failed. However, a no. 10 F. catheter finally entered the meatus and was easily passed to the bladder. Approximately 120 cc. (4 ounces) of normal urine was obtained. After catheterization another roentgenogram revealed relief of the previous distention of the urinary bladder. The urethral meatus was then dilated by a no. 12 bougie, after which the baby voided at normal intervals. Catheterization proved that there was no retention.

Eighteen hours after catheterization and dilation of the urethral meatus, the symptoms of drowsiness, anorexia, projectile vomiting and edema had disappeared. During this time the child frequently voided unusually large amounts of urine. This favorable course continued, and three days after the stricture of the urethral meatus was relieved, the patient was normal and remained so.

## COMMENT

While no chemical studies of the blood were made in the first case, it is considered noteworthy that the blood of the second patient, examined at the height of the symptoms, revealed no abnormal chemical conditions other than slight diminution of the serum protein level. One would surmise that some retention of nitrogenous substances should have occurred in the presence of such severe symptoms of intoxication. Because this was not observed and because of the rapidity of onset and disappearance of the symptoms, I suggest that this syndrome may result from an abnormal reflex function of the autonomic nervous system.

## SUMMARY

The clinical courses of 2 similarly afflicted newborn infants who had projectile vomiting, anorexia, drowsiness and edema during their first weeks of life are reported. Obstruction of the upper part of the intestinal

tract was suspected in each instance. However, roentgenographic examinations revealed marked dilatation of the urinary bladder, which was not relieved by voiding. Partial obstruction of the meatus of the urethra was discovered in each instance. Simple dilation of the stricture was followed by the complete disappearance of symptoms and the prompt recovery of each patient. In the second case, chemical examination of the blood was performed at the height of the symptoms, and no retention of nitrogen was found.

It is strongly urged that those in charge of newborn infants bear this possibility of urinary obstruction in mind when faced with symptoms which point prominently to gastrointestinal obstruction.

# Progress in Pediatrics

## ADRENOCORTICAL OBESITY IN CHILDREN

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The adrenogenital syndrome in children has been described and reviewed repeatedly (Bullock and Sequeira;[1] Glynn;[2] Reilly, Lisser and Hinman[3]). Most observers have been especially interested in the sexual precocity or pseudoprecocity caused by hypertrophy, adenoma or cancer of the adrenal cortex. Useful hypotheses have been advanced to explain the syndrome (Krabbe,[4] Grollman[5]), and progress has been made in its early diagnosis and treatment; but with few exceptions (Weber;[6] Guthrie and Emery[7]) little attention has been given to other symptoms which frequently accompany this form of precocity or pseudoprecocity.

Obesity and elevation of blood pressure were the outstanding symptoms in a child with an adrenocortical tumor observed by us. It seems worth while to direct special attention to these symptoms, in view of the physiologic, pathologic and diagnostic problems involved.

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1. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **56**:189-208, 1905.

2. Glynn, E. E.: Adrenal Cortex, Its Rests and Tumours: Its Relation to Other Ductless Glands, and Especially to Sex, Quart. J. Med. **5**:157-192, 1911-1912.

3. Reilly, W. A.; Lisser, H., and Hinman, F.: Pseudo-Sexual Precocity: The Adrenal Cortical Syndrome in Preadolescent Girls; Report of a Successfully Operated Case, Endocrinology **24**:91-114 (Jan.) 1939.

4. Krabbe, K. H.: Relation Between Adrenal Cortex and Sexual Development, New York M. J. **114**:4-8 (July 6) 1921.

5. Grollman, A.: Adrenals, Baltimore, William Wood & Company, 1936.

6. Weber, F. P.: Precocious General Development and Obesity, Proc. Roy. Soc. Med. **28**:149 (Dec.) 1934.

7. Guthrie, L., and Emery, W. de E.: Precocious Obesity, Premature Sexual and Physical Development, and Hirsuties in Relation to Hypernephroma and Other Morbid Conditions, Tr. Clin. Soc. London **40**:175-202, 1907.

Adrenocortical obesity is relatively rare in children, but it is of great general interest for the entire problem of endocrine obesity. The existence of "pituitary obesity" is still contested. The fact that tumors of the pituitary gland are accompanied by obesity in certain patients has led to the conclusion that this obesity is the result of the hormonal activities of the tumors. This conclusion, however, has not been generally accepted, since clinical results similar to those caused by pituitary tumors have been seen in patients who had foreign bodies, traumatic or inflammatory lesions or tumors of nonpituitary origin near or in the diencephalon. Therefore, many investigators are of the opinion that the pituitary genesis of obesity has not been proved and that the term "cerebral obesity" should be used in such cases instead of "pituitary obesity." It is obvious that such a controversy is due to the close spatial relation of the pituitary body and the vegetative centers of the hypothalamus.

The fact that tumors of the adrenal cortex, an endocrine gland far removed from these nervous centers, are seen in extremely obese patients and that removal of such tumors results in disappearance of the obesity suggests definitely an endocrine causation of at least this form of obesity. The importance of considering such cases in the discussion of the entire question of obesity of endocrine origin is obvious.

As a rule adrenocortical obesity is easily differentiated from other forms of adiposity. The enormous accumulation of fat around the face and on the upper parts of the trunk ("buffalo type of obesity") in a patient whose extremities are relatively free of fat is often indicative of a tumor of the adrenal cortex. However, similar tumors have been found in patients whose fat distribution was less typical and whose obesity could be confounded with forms seen in adiposogenital dystrophy, obesity of pineal origin and the like. It is obvious that the differentiation of these various forms of obesity is of great clinical importance, since their prognoses and treatment are different. To what extent the differential diagnosis can be based on the type of obesity alone and how far associated symptoms must be considered will be discussed in this paper.

Hypertension in children with adrenocortical tumors has been observed repeatedly. In about 20 per cent of the cases reviewed by Reilly, Lisser and Hinman, the blood pressure was abnormally high for the patient's age. Their review included cases of obese and of nonobese patients. Apparently, this percentage is higher if the obese type of patient with adrenal tumor is separately considered, as was done in our review. Since the relation of adrenal cortex to the regulation of blood pressure is still under discussion, clinical observations on this point appear to be of special interest.

REPORT OF A CASE

M. L., a girl, was born on April 3, 1939. The course of the pregnancy was normal, and the delivery was spontaneous. The child's birth weight was 6½ pounds (2,948 Gm.). The father was 24 and the mother 23 years of age when the child was born. They were healthy and had an older, healthy child. The family history was essentially noncontributory.

The child was apparently normal after birth. She was breast fed for eleven months; cereals and vegetables were added at 4 months of age and orange juice at 7 months. At the age of 3 months the infant's appetite became ravenous, and she began to gain weight rapidly. Her cheeks became red and her voice harsh. At the age of 6 months she had erysipelas. She recovered, and the obesity continued to increase.

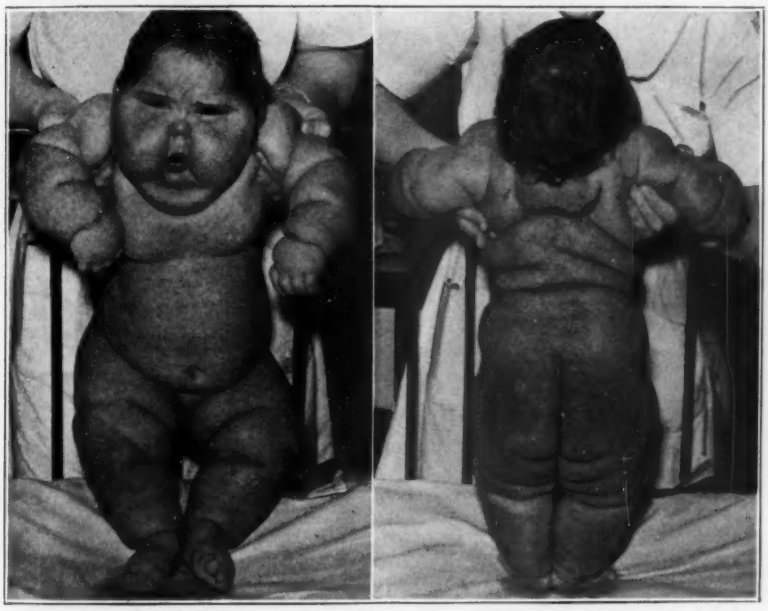

Fig. 1.—M. L. at the age of 10½ months.

At the age of 10½ months she was examined by one of us (T. M. M.). The child appeared excessively obese (fig. 1). The skin was remarkably red, especially on the cheeks, and on the legs was slightly cyanotic and somewhat mottled. There was a luxuriant growth of soft brown hair over the head. On the forehead, cheeks, back and pubes an abnormal amount of brown hair was seen, nowhere over 2 cm. in length. There was no axillary hair. The labia majora, the labia minora and the clitoris appeared normal. No abdominal mass could be palpated. The fundi appeared normal. The blood pressure was 200 mm. of mercury systolic and 110 diastolic. The child had a low grade fever during an observation period of ten days. She did not seem to have pain, and her mentality was apparently normal. She was unable to raise herself to the sitting position but could maintain the position when helped to assume it.

The child was referred to the Children's Hospital of Cincinnati, with a tentative diagnosis of adenoma of the adrenal cortex.

She was then 11 months old and weighed 12.5 Kg., but she appeared much heavier. Her height was 65 cm. Figure 1 shows the enormous fat pads of the cheeks, the chin and the shoulders. In addition, it shows the fat in the mammary and the abdominal regions and on the extremities. The accumulation of fat in the latter places is emphasized, because it is not characteristic for the "buffalo type" of obesity, which is said to be the type of obesity usually associated with adrenal tumors. Only 5 teeth were erupted. The physical findings were essentially the same as already mentioned, and her blood pressure was estimated as 245 mm. of mercury systolic and 145 diastolic. Roentgenograms of the skull and the sella turcica were normal. Roentgenograms of the long bones showed no osteoporosis or metastasis: the ossification was normal for the child's age. Attempts were made to take intravenous pyelograms, but the kidneys could not be visualized.

*Laboratory Data.*—The urine was normal. The red blood cell count was 5,830,000 cells per cubic millimeter, and the hemoglobin content was 15.4 Gm. per hundred cubic centimeters. The white blood cell count was 13,500 cells per

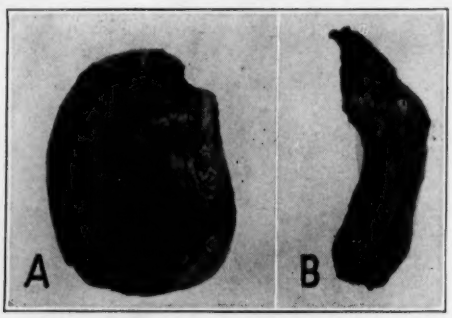


Fig. 2.—Adrenals from patient with adrenocortical obesity. *A*, right adrenal and tumor; *B*, normal left adrenal.

cubic millimeter. The urea nitrogen of the blood was 13 mg. per hundred cubic centimeters; the cholesterol of the whole blood was 110 mg. and that of the serum was 114. During a dextrose tolerance test the blood sugar rose from a fasting level of 107 mg. per hundred cubic centimeters to only 109 mg. one-half hour after the ingestion of dextrose, to 109 mg. after one hour, to 110 mg. after two hours, and to 113 mg. after three hours. The ascorbic acid content of the blood was 0.78 mg. and the inorganic phosphorus 3.4 mg. per hundred cubic centimeters. The carbon dioxide–combining power of the blood was 52 volumes per cent. The chloride content of the serum was 107.2 milliequivalents per liter; the sodium content, 141.8 milliequivalents; the potassium content, 4.7 milliequivalents, and the total base, 157.2 milliequivalents.

The reactions to the tuberculin and the Kahn test were negative.

*Course in the Hospital.*—The child had intermittent fever and showed signs of an infection of the upper respiratory tract. Her appetite had markedly diminished. She lost about 1 pound (454 Gm.) during her stay in the hospital. She was definitely susceptible to infections of the skin.

All observers concurred in the diagnosis of tumor of the adrenal cortex, but because of the great risk involved in carrying out an exploratory surgical pro-

cedure in an infant with such marked hypertension, it was thought advisable to defer operation until further attempts had been made to "lateralize" the tumor.

On April 6, 1940, high fever, cyanosis and dyspnea developed, and the patient died nine hours later. Apparently, the terminal complication was pulmonary edema caused by cardiac failure.

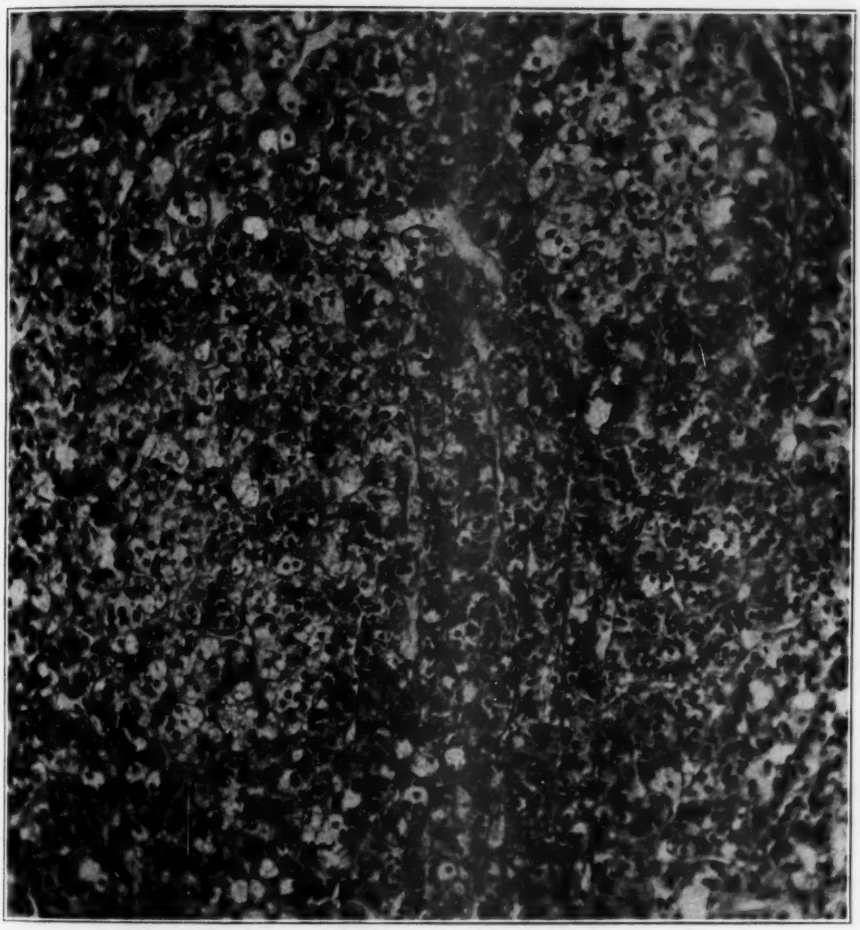

Fig. 3.—Photomicrograph, showing strands of small and nests of large, foamy, well differentiated tumor cells.

*Autopsy* (Dr. Ralph J. Johansmann).—The panniculus adiposus was extremely thick, measuring 2 to 3 cm. in the midline incision.

A soft spherical mass, measuring 3 cm. in diameter, was found in the region of the right adrenal gland. It was well encapsulated in a thin fibrous envelop. The right adrenal gland was identified along one border of this mass and was adherent to its capsule. The gland measured approximately 30 by 4 by 1 mm. The tumor and gland together weighed 12 Gm. (fig. 2). Section of the tumor revealed soft, yellow to yellowish tan tissue, throughout which were scattered

numerous hemorrhagic streaks and dots and several small gray cystic areas, the latter measuring not more than 2 mm. in diameter. There was no invasion of the capsule. The adrenal gland on section consisted of a thin, yellow cortex and an extremely thin, pale gray medulla. The left adrenal gland weighed 2.5 Gm. and measured 30 by 5 by 3 mm. Section showed a thin yellowish tan cortex and a gray medulla.

The ovaries, oviducts and uterus were apparently in normal relation. The small, pale pink ovaries measured 20 by 5 by 3 mm. The oviducts were not remarkable. The uterus was small and had a pale, pink, firm musculature. The vagina was smooth, white and glistening. Two small fenestrations were present in the hymen. The clitoris was not enlarged.

The pituitary was of average size and normal contour. The thymus was small, measuring 1.5 by 1 by 5 cm., and showed on section a pale red and flabby tissue. The thyroid, the pancreas, the spleen and the kidneys were normal. The liver weighed 405 Gm. Section showed a moderately swollen, yellow, greasy and slightly friable substance, speckled in certain areas with innumerable red dots. The brain weighed 550 Gm. Superficially there were marked flattening of the convolutions and narrowing of the intervening fissures. The heart weighed 37 Gm. The epicardium, the endocardium and the valves were normal. The aorta was normally elastic and had a smooth, yellow and glistening intima. There were signs of acute pulmonary emphysema, pulmonary atelectasis and aspiration of the contents of the stomach into the bronchial tree.

*Histologic Examination.*—The neoplasm of the right adrenal gland was composed of a mass of apparently well differentiated, rounded and polyhedral epithelial cells with relatively large spherical and oval nuclei, in appearance and arrangement resembling in large measure normal adrenal cortex. The cells were fairly uniform in size and were arranged in nests, in columns and in irregular aciniform structures. The groups were separated from one another by fine strands of vascular connective tissue. In some areas the cells were slightly larger and had a vacuolated, foamy cytoplasm (fig. 3). There were no evidences of anaplasia, and no mitotic figures were seen. A few small areas of coagulation necrosis, with associated hemorrhage and cyst formation, were present throughout the tumor mass.

The entire neoplasm was well encapsulated. Although the capsule varied in thickness and in some portions was thin, no part of it showed infiltration by tumor cells (fig. 4). A thinned strip of apparently normal, although compressed, adrenal tissue lay external to and almost completely surrounding this capsule. The cells of the normal tissue were slightly smaller than the tumor cells, did not possess their foamy characters and more closely resembled the cells of the normal left adrenal gland. The medullary portion of this strip of adrenal gland was thin but otherwise appeared normal. Ponceau-fuchsin stains used according to the modified technic of Fujiwara [8] failed to demonstrate the presence of androgenic adrenal cortical cells in the tumor.

The thyroid, the thymus and the ovaries showed no histologic changes, and the pancreas was not remarkable except for a slight invasion by adipose tissue. Serial sections of the pituitary revealed a slight increase in the number of acidophilic compared with basophilic cells.

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8. Fujiwara, T. F.: Ponceau-Fuchsin Stain for Androgenic Adrenal Cortical Cells, Arch. Path. **27**:1030-1031 (June) 1939.

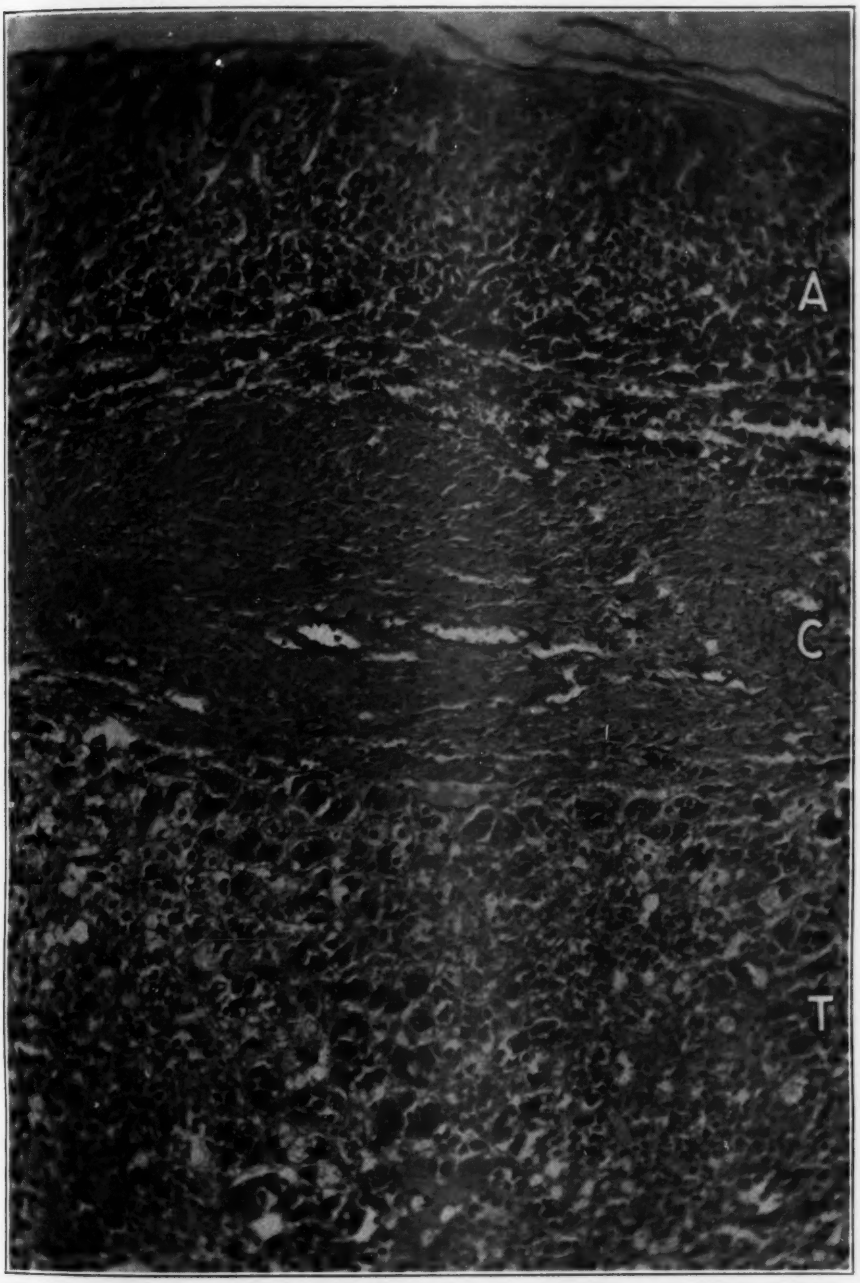


Fig. 4.—Photomicrograph, showing the compressed but otherwise normal right adrenal (*A*), the fibrous capsule which enveloped the tumor (*C*) and the tumor (*T*).

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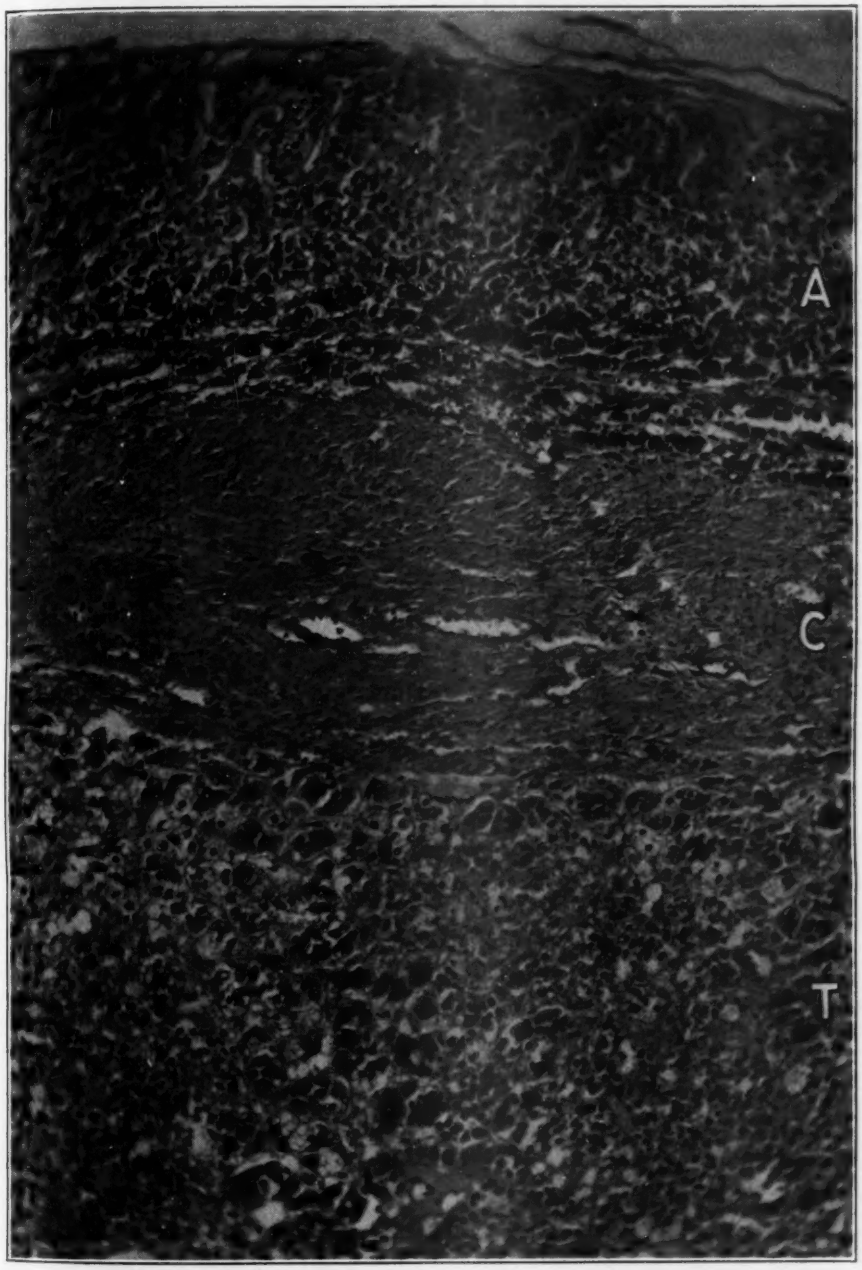


Fig. 4.—Photomicrograph, showing the compressed but otherwise normal right adrenal (*A*), the fibrous capsule which enveloped the tumor (*C*) and the tumor (*T*).

The pulmonary capillaries were markedly congested, and in focal areas the alveoli were filled with an inflammatory exudate consisting of macrophages and polymorphonuclear leukocytes. There were also numerous focal areas of acute emphysema.

*Pathologic Diagnoses.*—These were: adenoma of the cortex of the right adrenal gland; hirsutism and marked obesity; acute tracheitis and bronchitis, with small areas of lobular pneumonia and acute tracheobronchial lymphadenitis; aspiration of foreign material into the bronchial tree, probably terminal; acute emphysema; acute congestion of the lungs, the liver, the spleen and the kidneys; severe fatty infiltration of the liver; toxic myocarditis and nephrosis; mild acute enteritis and mesenteric lymphadenitis, and slight fatty invasion of the pancreas.

The most striking symptoms in this patient were a monstrous obesity and a very high blood pressure. Sexual pseudoprecocity or virilism was not fully developed, although the presence of pubic hair and the deep voice indicated that abnormal development toward masculinization had begun in this child.

## OBSERVATIONS ON OBESE CHILDREN WITH TUMORS OF THE ADRENAL CORTEX

The question arose whether obesity and hypertension alone are indicative of a tumor of the adrenal cortex. To find an answer to this question, 24 cases of obesity in children with tumors of the adrenal cortex were collected from the literature and reviewed, and with data from them the accompanying table was compiled. In addition, some of the etiologic factors and symptoms of this disease picture have been considered individually, and its treatment and final outcome will be discussed.

*Age.*—Obesity may begin or occur at any age. However, as the table indicates, pathologic symptoms are noted in the majority of patients during infancy and early childhood. None of the patients considered in this study was born obese. The earliest onset of obesity was recorded in a boy 11 weeks old (Lightwood [9]) and in our patient, who showed obesity at the age of 3 months. Only 2 patients were reported on (Bullock and Sequeira; [1] Kennedy and Lister [10]) whose symptoms began relatively late in childhood, that is, at the ages of 10 and 12½ years respectively. After puberty the incidence of adrenocortical obesity seems to increase, but children in this age group were not included in this study.

*Sex.*—Girls are more often affected than boys. There were only 3 boys among the 24 patients for whom data are given in the table. The sex ratio is thus 7 girls to 1 boy.

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9. Lightwood, R. C.: Tumour of the Suprarenal Cortex in an Infant of Eighteen Weeks, Arch. Dis. Childhood **7**:35-42 (Feb.) 1932.

10. Kennedy, C. M., and Lister, W. A.: Case of Suprarenal Hypernephroma, Lancet **2**:749-751 (Oct. 8) 1927.

*Family History.*—The family history was found to be essentially noncontributory in the majority of the cases. Two children related to van der Bogert's [11] patient were said to have shown sexual precocity, but this statement was not verified. A deep voice was noted in the mother of Collett's [12] patient. The convulsions of the mother during pregnancy mentioned in 1 case (Ogle [13] and Pitman [14]) are probably of little significance in this connection.

*Past History.*—Postnatal factors apparently contribute little to the development of this disease. Therefore, the past history of the children affected appears irrelevant in most respects. In 1 patient (Guthrie and Emery [7]) the onset of symptoms followed measles. Another child (van der Bogert [11]) had had convulsions since birth.

*Obesity.*—The "buffalo type" is said to be characteristic for obesity of adrenal origin. The accumulation of fat on the cheeks and chin and the obesity of the upper parts of the trunk, with relative lack of fat on the extremities, give many of the patients a typical appearance. Accordingly, some children of this type can be recognized at a glance. However, in other patients the fat distribution is less characteristic. The girl observed by us showed in addition to extreme obesity of face and trunk marked adiposity of the limbs and abdomen. In some girls of the age of prepuberty, the abnormal distribution of fat caused by an adrenocortical tumor may resemble that in patients with adiposogenital dystrophy.

In spite of their monstrous appearance the actual weight of the children with tumors of the adrenal cortex may not be much greater than the average. Thus, the obese child in the case reported by Gross [15] was of normal weight for her age and height; fat pads were seen in the face and on the upper part of the thorax of an infant described by Lightwood [9] who showed general wasting. The greatest increase in weight (26 Kg.) was recorded in the case of Moltchanoff and Davydovsky,[16] but in this case there was pituitary and cerebral involvement.

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11. van der Bogert, F.: Virilism and Hypertension in Infancy Associated with Adrenal Tumor, J. Pediat. **3**:629-634 (Oct.) 1933.

12. Collett, A.: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am. J. Dis. Child. **27**:204-218 (March) 1924.

13. Ogle, J. W.: Unusually Large Mass of Carcinomatous Deposit in One of the Suprarenal Capsules of a Child, Tr. Path. Soc. London **16**:250-252, 1864-1865.

14. Pitman: General Melasma and Short Hair Over the Entire Body of a Child of Three Years with Conversion of the Left Suprarenal Capsule into a Large Malignant Tumor, the External Organs of Generation Resembling Those of Adult Life, Lancet **1**:175, 1865.

15. Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood, Am. J. Dis. Child. **59**:579-628 (March) 1940.

16. Moltchanoff, V. I., and Davydovsky, I. V.: Zur Klinik und Entstehungsweise des Hirsutismus, Virchows Arch. f. path. Anat. **274**:606-632, 1930.

| Author and Year of Publication | Age* and Sex | Age* at Onset | Obesity, Weight, Appetite | Height, Cm. | Genitalia | Blood Pressure, Mm. Hg | Abnormal Growth of Hair | Skin |
|---|---|---|---|---|---|---|---|---|
| Cooke, E., 1756; cited by Bullock and Sequeira [1] | 7 F | .. | Enormously fat | Tall | ..... | ..... | On face and genitalia | ..... |
| Bevern and Römhild, 1802: cited by Neurath, R.: Ergebn. d. inn. Med. u. Kinderh. 4: 46-81, 1909 | 3½ F | .. | Fat | ... | ..... | ..... | On face and genitalia | ..... |
| Tilesius, 1803; cited by Bullock and Sequeira [1] | 4 F | .. | Fat | 80 | ..... | ..... | On genitalia | ..... |
| Ogle [13] and Pitman,[14] 1805 | 3 F | 2 | Fat; 20 Kg. | 86 | Large and well developed; internally normal | ..... | Generalized, especially on genitalia; heavy eybrows; moustache | Dark but not bronzed |
| Dickinson, W. H., cited by Bullock and Sequeira[1] | 3 F | 1 | Enormous appetite | ... | ..... | ..... | Generalized | Dark but not bronzed |
| Fox,[15] 1885 ..... | 2 F | 10 mo. | Gross and bloated; ravenous appetite | ... | Clitoris enlarged; vulva precociously developed | ..... | On trunk and genitalia | Dusky |
| Bullock and Sequeira,[1] 1905 | 11 F | 10 | Large face, 45 Kg. | 135 | Clitoris, uterus enlarged; menstruation at 10 yr. | Definitely raised | On lip, chin, axillas, genitalia | Atrophic striae on abdomen and thighs |
| Guthrie and Emery,[7] 1907 | 4¾ M | 2 | Obese, chiefly in face, trunk, upper extremities, not below sacrum; 22 Kg. | 90 | Normal | ..... | Bushy eyebrows; moustache; on face, back, genitalia | Cheeks bright red |
| Walker, cited by Richards, O.: Guy's Hosp. Rep. 59: 217-232, 1905 | 8½ F | 5 | Stout up to 8th year | ... | ..... | ..... | On face, chin, genitalia | ..... |
| Glynn,[2] 1912 ..... | 5 F | 3 | Fat and flabby | Tall | Clitoris not enlarged; no menstruation | ..... | On face, back, genitalia | Acne |
| Collett,[12] 1924 ..... | 1½ F | 8 mo. | Bulging cheeks, short neck, short extremities; 15 Kg. | 80 | Clitoris penis-like; hypospadias; labia and mons veneris well developed; vagina, uterus normal | ..... | On face, trunk, thighs, genitalia | Rough |
| Kennedy and Lister,[10] 1927 | 13 F | 12½ | Fat chiefly in face and on trunk, less on extremities; 49 Kg. | 135 | Clitoris not enlarged; labia enlarged; no menstruation | ..... | On face, shoulders, back, genitalia | Florid; purple striae on buttocks, hips and abdomen |
| Lundh, G.: Acta pædiat. 9: 118-128, 1929 | 3½ F | 3 | Fat; ravenous appetite | 93 | Clitoris 3 cm. long, with prepuce and hypospadias; external genitalia well developed; discharge; no menstruation | ..... | On lower half of body, genitalia | ..... |
| Fordyce and Evans,[17] 1929 | 2½ M | 6 mo. | Generalized obesity; 19 Kg. (at 8 mo.; 21 Kg.) | 85 | Large penis and testes | 80/50 | Generalized | Acne; florid |
| Moltchanoff and Davydovsky, 1930 | 6 F | 4 | Fat, particularly in face and on trunk; 35 Kg. | 119 | Clitoris 3 cm. long; labia, vagina large | 145 | Generalized, especially on face, linea alba, genitalia | Red; increased perspiration of bad odor; purple striae |
| Schweizer, F.; Senet, O., and Llambias, A.: Arch. argent. de pediat. 1: 550-556 (Nov.) 1930 | 7 F | 6½ | Hard fat pads in face, extremities not very fat; 28.6 Kg. | 114 | Clitoris enlarged (2 cm.); labia enlarged | 150/90 | Generalized, especially on genitalia | Bright red cheeks; acne |

* In years unless noted.

| ther rvations | Mentality | Roentgenologic Data | Laboratory Data | Treatment | Outcome |
|---|---|---|---|---|---|
| ..... | ..... | ..... | ..... | ..... | Death. Autopsy: tumor extended below liver from pole of one kidney to other kidney; encephalomalacia; hydrocephalus internus |
| ..... | ..... | ..... | ..... | ..... | Death. Autopsy: large tumor in region of spleen and left curvature of colon |
| is enlarged | ..... | ..... | ..... | ..... | Death. Autopsy: tumor of left adrenal size of goose egg; metastases to liver |
| r palpable side of nen | ..... | ..... | ..... | ..... | Death. Autopsy: tumor of left adrenal cortex; metastases to liver |
| ..... | Dull | ..... | ..... | ..... | Death. Autopsy: large tumor of adrenal cortex; metastases to liver |
| r in abdo- abnormal | Dull | ..... | ..... | ..... | Death. Autopsy: sarcoma (?) of left adrenal; right adrenal not found; metastases to lung |
| r in left hondrium; n abdomen | ..... | ..... | Albumin in urine | ..... | Death. Autopsy: carcinoma of left adrenal; metastases to liver and lungs; right adrenal somewhat enlarged |
| lsions before nation; ulosis | Precocious, bright | ..... | ..... | ..... | Death. Autopsy: tumor (carcinoma ?) size of walnut over left kidney; neither adrenal found; died of tuberculosis |
| r in left hondrium; | ..... | ..... | Albumin in urine | ..... | Death. Autopsy: left kidney size of coconut; right kidney nearly destroyed by growth; adrenals not mentioned |
| r in right f abdo- convulsions ially | Bright; later dull | ..... | ..... | ..... | Death. Autopsy: tumor of right adrenal cortex; no metastases but infiltration of small veins |
| r in left f abdo- | Slightly precocious | Advanced osseous development | ..... | Operation: tumor (hypernephroma of left adrenal cortex) removed at age of 2 yr. 2 mo. | Striking improvement |
| r in left hondrium; thin, tapering | Average | ..... | Glycosuria on one occasion | Operation: tumor of left adrenal removed | Death 36 hr. after operation. Autopsy: hypernephroma of left adrenal cortex; right adrenal small; metastases in lungs |
| r in left f abdo- | Became fretful and troublesome | ..... | ..... | ..... | Death. Autopsy: tumor of left adrenal cortex size of man's head |
| muscular th; spleen ble; urine ntly ng | ..... | Ossification normal | Trace of albumin in urine | Operation: tumor (size of orange) removed from left adrenal | Death 12 hr. after operation. Autopsy: right adrenal small; metastases to liver and brain |
| r in right f abdomen; en large; nlarged; ulosis; aresis and trophy | Normal | Ossification advanced | 0.2% dextrose in urine | ..... | Death. Autopsy: adenoma of right adrenal cortex; colloidal cyst of pituitary; encephalomalacia; cystic degeneration of ovaries; miliary tuberculosis; septicemia |
| en en- ; pain in lank; palpable t flank; ral circu- on right abdomen ; pollak- | ..... | Tumor visible on flat plate of abdomen; pyelography showed deformity of right kidney | ..... | Operation: tumor (size of orange) removed from right adrenal | Death from postoperative hemorrhage and shock on day of operation. Autopsy: tumor invading kidney; metastases to lungs; ovaries of adult size; thyroid atrophic |

| Author and Year of Publication | Age* and Sex | Age* at Onset | Obesity, Weight, Appetite | Height, Cm. | Genitalia | Blood Pressure, Mm. Hg | Abnormal Growth of Hair | Skin |
|---|---|---|---|---|---|---|---|---|
| Birrell, J. A.: Bristol Med.-Chir. J. 49: 119-122, 1932 | 5 F | 4 | Generalized obesity | ... | Clitoris and labia enlarged | 135/80 | Generalized, especially on cheeks | Acne |
| Lightwood,[9] 1932 ..... | 4½ mo. M | 11 wk. | Fat in cheeks, on chin, upper part of thorax, with general wasting | ... | Normal | ..... | Bushy eyebrows; on forehead | Florid cheeks |
| Van der Bogert,[11] 1933 | 2 F | 9 mo. | Generalized obesity; 17½ Kg. | ... | Clitoris enlarged; vulva prominent | 160/110 | Generalized, especially on face, genitalia; heavy eyebrows | ..... |
| Walters, Wilder and Kepler,[26] 1934 | 9 F | 4 | Fat in face, on neck and trunk; 49 Kg. | 133 | Clitoris enlarged (?); external genitalia well developed; menstruation at 8 yr. | 132/97 | Generalized, especially in axillas and on genitalia | Acne; purple striae |
| Little,[27] 1936 ..... | 7½ F | 3½ | Fat in face, on upper part of trunk; waist, arms and legs thin | ... | Clitoris enlarged; external genitalia large, uterus small | 120/80 | Generalized, especially on face, eyebrows, mons veneris | ..... |
| Crooke and Callow,[23] 1939 | 6 F | 6 | Obesity of face, neck, abdomen; limbs normal; rapid gain from 22 to 40 Kg. | ... | Clitoris, labia enlarged | 150/120 180/145 | On genitalia; later, generalized | Acne; purple striae |
| Gross,[15] 1940 ..... | 3¼ F | 3 | Obesity began in face and on extremities; later, entire body involved; 15 Kg. | 96.5 | Normal | 190/160 260/190 | ..... | Plethoric |
| Marks, Thomas and Warkany, 1940 | 11 mo. F | 3 mo. | Generalized obesity, especially on cheeks, chin, extremities; 12.5 Kg. | 65 | Clitoris not enlarged; labia majora large | 245/145 200/110 | Some on cheeks, forehead, back and genitalia | Red |

*Height.*—Of the 24 patients for whom data are included in the table, 4 were tall, 5 normal and 6 subnormal in height. Data concerning the height of the remaining 9 patients were not available. Thus, gigantism does not always accompany adrenocortical obesity.

*Genitalia.*—It has been asserted that adrenocortical tumors cause sexual precocity in boys and pseudoprecocity in girls. This statement is not entirely borne out by the data for the 24 obese patients in whom adrenal tumors were found. An enlarged clitoris was noted in 11 of the 21 girls. Sometimes the clitoris was described as penis-like and the prepuce as well developed. Hypospadias was described in several cases. In 5 girls a normal clitoris was observed, but in 3 of these some precocious development of the vulva was recorded. In only 2 girls were the genitalia reported to be normal. Precocious menstruation

*n with Tumors of the Adrenal Cortex—Continued*

| ther vations | Mentality | Roentgenologic Data | Laboratory Data | Treatment | Outcome |
|---|---|---|---|---|---|
| nd spleen le | Dull; listless and silent | ..... | ..... | ..... | Death. Autopsy: tumor of left adrenal cortex, replacing gland and destroying much of left kidney; metastases to liver |
| n left | ..... | ..... | 4,000 normoblasts per cu. mm. | ..... | Death. Autopsy: cortical adenoma (benign hypernephroma) of left adrenal |
| r on right abdomen; nlarged ; tortu- of retinal ; convul- ince birth | ..... | Sella turcica small; lower epiphysis of femur ragged | Trace of albumin in urine | Operation: tumor of right adrenal removed | Death 36 hr. after operation. Both adrenals large, right larger than left; tumor: cortical carcinoma |
| s de- d at 4 yr. | Normal, but shunned company of other children | Sella turcica normal; no shadow of thymus; ossification advanced; pyelogram normal | Basal metabolic rate,—20%; dextrose tolerance test normal; glycosuria on one occasion | Operation: encapsulated tumor (cortical adenoma) removed; right adrenal one half normal size | Striking improvement |
| inal headache; sions; lar weak- oderate orosis | ..... | Calcified mass in left upper abdominal quadrant; sella turcica normal; moderate osteoporosis; pyelogram; distortion of pelvis of left kidney | Trace of albumin in urine | Thyroid, ovarian preparations; some improvement | Death. Autopsy; carcinoma of left adrenal cortex; metastases to liver and lungs |
| in left ain; abdo- larged; ed muscu- ength; nlarged | ..... | Ossification normal | Albumin in urine | ..... | Death. Autopsy: large tumor replacing left adrenal and invading kidney; carcinoma of adrenal cortex; metastases to liver and lymphatic glands; pituitary: basophils showed hyaline degeneration |
| isions; l atrophy; nlarged; tapering; reacted hly | Dull | Encephalogram showed enlarged lateral ventricles; ossification retarded | Basal metabolic rate, —37% | ..... | Death. Autopsy: carcinoma of left adrenal cortex |
| ed heart | Normal | Sella turcica normal; ossification normal; no osteoporosis | Dextrose tolerance curve flat | ..... | Death. Autopsy: cortical adenoma of right adrenal; cardiac hypertrophy |

was present in 2 patients. Of the 3 boys for whom data are included in the table, 2 had normal external genitalia, but the abnormal growth of hair indicates some precocious development in these patients.

*Hirsutism.*—Abnormal growth and distribution of hair is one of the most constant findings in the patients with adrenal obesity. It was noted in some form in all but one of the patients for whom data are listed in the table. Many times generalized hypertrichosis was noted, but this is a symptom also seen frequently in a variety of other abnormal conditions and is therefore of little diagnostic value. Of greater importance is the appearance of long hair on the face (forehead, upper lip and chin), on the trunk (axillas, shoulders, chest and back) and in the pubic region. Heavy, masculine eyebrows contribute to the characteristic picture. It is possible that death may occur before the abnormal distribution of hair becomes evident.

*Skin.*—The skin is described as dark and dusky by some authors, while a highly red color was pointed out by others. The plethoric appearance of the cheeks is striking in many cases and contributes to the strange appearance of these children. Purplish striae on the hips, abdomen and thighs are seen mainly in the older girls affected. Acne is a frequent finding even in very young children.

*Voice.*—With the development of the disease a change of voice occurs frequently. In the fully developed syndrome a deep, harsh or coarse voice is noted. Changes of the larynx caused by the "hormone of masculinization" are probably responsible for the change of voice, which may precede other symptoms of masculinization.

*Blood Pressure.*—Hypertension was a frequent symptom in children with adrenal obesity and was indicated by the plethoric appearance, the enlargement of the heart to the left and the occurrence of cerebral hemorrhages. In the children whose blood pressure was measured, an elevation was regularly found, with one exception (Fordyce and Evans [17]). For a patient reported on by Gross [15] and for our patient the readings were particularly high.

*Other Observations.*—In many patients an abdominal tumor may be palpable and abdominal pain may be present. In other patients, however, the tumor may be too small to be felt through the obese abdominal walls and yet cause marked endocrinologic changes. Enlargement of the abdomen, with ascites, may be seen in advanced stages. The liver is palpable in some patients owing to displacement by the tumor or to enlargement by metastases. Disturbances of micturition have been observed. Convulsions may occur, and sluggish reaction of the pupils to light was observed in 1 case. Tortuosity of the retinal vessels has been described. Unusual muscular development was pointed out by several authors. The high blood pressure may lead to cerebral accidents, and paralysis may occur subsequently. Abnormal thirst was recorded only once (Fox [18]). Possible congenital hemiatrophy in 1 patient (Moltchanoff and Davydovsky [16]) is of great interest, since hemiatrophy and hemihypertrophy have previously been found in patients with adrenal tumors (Hutchison [19]; Harwood and O'Flynn [20]).

17. Fordyce, A. D., and Evans, W. H.: Suprarenal Virilism, with Report of Two Cases: Pathologic Notes, Quart. J. Med. **22**:557-566 (July) 1929.

18. Fox, T. C.: Case of Primary Sarcoma of the Left Suprarenal Capsule with Extensive Thrombosis of the Vena Cava Inferior in a Child, Tr. Path. Soc. London **36**:460-463, 1884-1885.

19. Hutchison, R.: Case of Hemi-Hypertrophy in Which the Internal Organs Were Affected, Brit. J. Child. Dis. **1**:258-260, 1904.

20. Harwood, J., and O'Flynn, E.: Specimens from a Case of Right-Sided Hemihypertrophy Associated with Pubertas Praecox, Proc. Roy. Soc. Med. **28**:837 (May) 1935.

In another patient with hemihypertrophy, calcium deposits were seen above both kidneys on roentgen examination (Kottmeier [21]). The coexistence of adrenal tumors with such congenital deformities seems of some significance.

*Mentality.*—The patients at first show normal mental development and are described in certain instances as bright, even precocious. But as the disease progresses, they frequently become listless, apathetic and dull.

*Laboratory Data.*—The blood findings are essentially normal. The count of the red blood cells and the determination of hemoglobin give, as a rule, high normal values. The blood sugar level and the results of the dextrose tolerance test are usually normal. Results of other chemical studies on the blood are essentially normal. The basal metabolic rate may be low. Albumin is frequently found in the urine. The tests of renal function give normal results. Transitory glycosuria was noted in 2 patients (Kennedy and Lister,[10] Moltchanoff and Davydovsky [16]). The diagnosis of the adrenocortical syndrome has been well supported in several cases by the determination of androgens in the urine of the patients (Broster and Vines [22]). The value of the method was well demonstrated by Crooke and Callow,[23] who examined 4 patients with the clinical picture of the Cushing [24] syndrome. In 2 of these patients a malignant adrenal cortical tumor was diagnosed clinically and its presence confirmed in 1 case by autopsy and in the other by operation. "The urine of these two patients gave high values in the colorimetric assay of 17-ketosteroids or in the biological assay of androgens. This increase of 17-ketosteroids was largely due to *trans*dehydroandrosterone which was isolated from the urine in amounts many times as great as those occurring in normal men and women. The other two cases, in which no adrenal tumour was present, gave low values by comparison in the colorimetric or biological assay." Dingemanse and Laqueur [25] found large quantities of cockscomb growth–stimulating substance in the urine of 3 patients with hypernephroma.

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21. Kottmeier, H. L.: Ueber Hemihypertrophia und Hemiatrophia corporis totalis nebst spontane Extremitätengangräne bei Säuglingen im Anschluss zu einem ungewöhnlichen Fall, Acta pædiat. **20**:530-541, 1937.

22. Broster, L. R., and Vines, H. W. C.: Note on Adrenal Cortex, Brit. M. J. **1**:662 (March 27) 1937.

23. Crooke, A. C., and Callow, R. K.: Differential Diagnosis of Forms of Basophilism (Cushing's Syndrome), Particularly by Estimation of Urinary Androgens, Quart. J. Med. **8**:233-249 (July) 1939.

24. Cushing, H.: Basophil Adenomas of Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**:137-195 (March) 1932.

25. Dingemanse, E., and Laqueur, E.: Occurrence of Abnormally Large Quantities of Male Hormone in Urine of Patients with Suprarenal Tumor, Nederl. tijdschr. v. geneesk. **82**:4166-4170 (Aug. 27) 1938.

*Roentgenologic Data.*—Roentgenograms of the skull are normal. The ossification as seen in the wrists is described as normal (Crooke and Callow,[23] Fordyce and Evans,[17] our case), advanced (Collett[12]; Walters, Wilder and Kepler;[26] Moltchanoff and Davydovsky[16]) or retarded (Gross[15]). Osteoporosis is absent in the majority of cases; only in Little's[27] case a moderate degree of it was noted. The lower epiphysis of the femur appeared ragged in the roentgenogram of 1 patient (van der Bogert[11]). Calcification of the adrenal region can be seen in flat plates of the abdomen (Little[27]). Intravenous pyelography may be helpful, since it may reveal displacement of one kidney by the tumor, but a normal pyelogram does not exclude adrenal involvement (Walters, Wilder and Kepler[26]). Perirenal insufflation of air may outline the tumor (Cahill[28]) but is a dangerous procedure (Weyrauch[29]).

*Differential Diagnosis.*—Adrenocortical obesity can be distinguished without difficulty, as a rule, from the adiposogenital dystrophies. The latter term is employed here to describe a variety of disease pictures, like the common adiposity of prepuberty and puberty and the rarer forms in which obesity and hypogenitalism are combined with mental deficiency and defects of the eye and skeleton (Laurence-Moon-Biedl and related syndromes). Since the site of the disorder causing the adiposogenital dystrophies is in all probability in the pituitary-hypothalamic region, it is necessary to distinguish them from the adrenocortical syndrome. This syndrome, it is said, is characterized by signs of sexual precocity or pseudoprecocity, while patients with the adiposogenital dystrophies show signs of hypogenitalism or delayed puberty. However, sometimes this differential point is not diagnostic, since normal genitalia may accompany either form of obesity or the condition of the genitals may not be easily recognized in a child. In such cases other criteria will have to be considered in the differential diagnosis.

Adrenocortical obesity is relatively rare between the ages of 8 and 12 years, and it is about seven times more frequent in girls than in boys; adiposogenital dystrophy is most often seen at the age before puberty and it occurs with equal frequency in the two sexes.

The absence of significant family histories in patients with adrenal obesity should be emphasized, since significant family histories are so frequently obtained for children with adiposogenital dystrophy. Other members of the families of the patients in this group may have obesity,

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26. Walters, W.; Wilder, R. M., and Kepler, E. J.: Suprarenal Cortical Syndrome, with Presentation of Ten Cases, Ann. Surg. **100**:670-688 (Oct.) 1934.

27. Little, A. A.: Carcinoma of the Adrenal Cortex, J. Pediat. **9**:62-67 (July) 1936.

28. Cahill, G. F.: Air Injections to Demonstrate Adrenals by X-Ray, J. Urol. **34**:238-243 (Sept.) 1935.

29. Weyrauch, H. M.: Death from Air Embolism Following Perirenal Insufflation, J. A. M. A. **114**:652-655 (Feb. 24) 1940.

hypogonadism or diabetes mellitus; and in the families of the patients of the Laurence-Moon-Biedl group mental retardation, ocular defects or skeletal anomalies may be present, while the families of the children with adrenocortical obesity for whom data are given in the table were conspicuously free of such anomalies.

The fat distribution of the "buffalo type" will facilitate the diagnosis in many cases. However, the extremities may also be markedly obese in patients with an adrenocortical tumor (our case), thus making the diagnosis uncertain. The general aspect of the child then may resemble that of a patient with any other type of obesity.

In the case of an infant there must also be considered in differentiation nutritional obesity or the adiposity seen in the Laurence-Moon-Biedl syndrome (Ornsteen,[30] fig. 4). The presence of polydactylism, syndactylism, retinitis pigmentosa or related defects will support the latter diagnosis and speak against a tumor of the adrenal gland.

It has been pointed out that hirsutism is one of the most constant symptoms of adrenocortical tumors; in adiposogenital dystrophy the appearance of facial, axillary and pubic hair is usually delayed.

The "rosy" cheeks seen in patients with adiposogenital dystrophy can be easily distinguished from the plethoric appearance of children with adrenal obesity. Striae are seen in either condition. Acne is suggestive of adrenocortical tumor when seen in early childhood; its presence at or near puberty is of little diagnostic value. A deep or harsh voice or definite hypertension in a young child is suggestive of adrenocortical tumor. The presence of local abdominal signs facilitates the diagnosis, but their absence does not exclude a tumor of the adrenal cortex. Demonstration of large amounts of androgenic substances in the urine will be helpful in the diagnosis of adrenocortical overactivity.

Tumors of the pineal gland and neoplasms of the interpeduncular region must be considered in the differential diagnosis, since their endocrinologic manifestations may resemble those of a tumor of the adrenal cortex. The sex of the patient may play an important role in the diagnosis, since—in contrast to adrenal tumors—pineal neoplasms cause sexual precocity apparently only in boys (von Frankl-Hochwart;[31] Bailey and Jelliffe[32]). Obesity due to pineal tumor has

30. Ornsteen, A. M.: Contribution to the Pathogenesis and Heredity of the Laurence-Biedl Syndrome (Dystrophia Adiposogenitalis, Retinitis Pigmentosa, Mental Deficiency and Polydactylism): Report of Three Cases in One Family, Am. J. M. Sc. **183**:256-268 (Feb.) 1932.

31. von Frankl-Hochwart, L.: Ueber Diagnose der Zirbeldrüsentumoren, Deutsche Ztschr. f. Nervenh. **37**:455-465, 1909.

32. Bailey, P., and Jelliffe, S. E.: Tumors of the Pineal Body with an Account of the Pineal Syndrome: The Report of a Case of Teratoma of the Pineal and Abstracts of All Previously Recorded Cases of Pineal Tumors, Arch. Int. Med. **8**:851-880 (Dec.) 1911.

been described in patients of either sex (Marburg [33]). It appears that the obesity found in such patients is usually moderate as compared with the monstrous obesity of children with tumors of the adrenal cortex. Unusual muscular strength and physical, particularly osseous, and mental precocity have been described in either condition. As a rule, a pineal tumor will be easily recognized by its neurologic manifestations, but it should be kept in mind that convulsions (Collett,[12] van der Bogert,[11] Little,[27] Gross [15]), sluggish reaction of the pupils (Gross [15]) and hemiparesis (Moltchanoff and Davydovsky [16]) have been noted in patients with adrenal tumors. It is understandable that a variety of neurologic symptoms may be present in such cases if there is complicating cerebral hemorrhage, encephalomalacia or internal hydrocephalus.

Moderate obesity and sexual precocity may also occur with tumors of the interpeduncular region of the floor of the third ventricle. Since only minimal, or no, signs of increased intracranial pressure may be present in such cases (Le Marquand,[34] Gross [15]) an adrenocortical tumor must be considered as the cause of such endocrinologic symptoms. In girls, the signs of maturation will assist in the differential diagnosis, since an interpeduncular tumor causes true precocity—development of the breasts and genitalia and occurrence of menstruation—while an adrenal tumor usually results in pseudoprecocity, with signs of masculinization. In boys, however, the sexual changes may be similar in the two conditions. Since elevation of the blood pressure may also occur in patients with either condition, the differentiation will sometimes be rather difficult.

It is well known that the symptoms of adrenocortical obesity and those found in certain patients with a basophilic adenoma of the anterior lobe of the pituitary gland (Cushing's syndrome) may resemble one another closely. However, to our knowledge, such pituitary adenomas associated with the Cushing syndrome have not been described as occurring in young children. It also appears that pluriglandular syndromes simulating Cushing's disease, which present difficult diagnostic and therapeutic problems when they occur in adults, are rather rare in children. But it should be mentioned here that children have been observed in whom a fully developed picture resembling adrenocortical obesity was present without an adrenal tumor or any other pathologic condition which could explain the syndrome. In a patient of Guthrie and Emery,[7] obesity and hirsutism were present, but the adrenal glands

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33. Marburg, O.: Zur Kenntnis der normalen und pathologischen Histologie der Zirbeldrüse; die Adipositas cerebralis, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **17**:217-279, 1908.

34. Le Marquand, H. S.: Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with Tumour in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep., 1934-1935, pp. 31-61.

were found normal at autopsy. In a girl described by Crooke and Callow,[23] obesity, hirsutism, elevation of blood pressure and enlargement of the heart suggested the diagnosis of adrenocortical tumor, but exploratory laparotomy showed no tumor in either adrenal gland (see also Ellis [35]). Such cases may possibly be explained by the fact that aberrant hypertrophic adrenal tissue may be found in such sites as the ovaries, the testes and the kidneys. A case of a girl, aged 3½ years, in whom signs of physical precocity had been noted and in whom a hypernephroma of the ovary was found at operation, was reported by Downes and Knox.[36] However, obesity was absent in this patient, as well as in the girl described by Gaudier,[37] who presented a picture of true precocity rather than pseudoprecocity. Such a picture resembles more the endocrine syndrome seen in children with granulosa cell tumor of the ovary. This syndrome consists of true sexual precocity and premature general physical development but does not lead to excessive obesity.

*Pathology.*—The tumors of 16 of the patients in the 24 cases reviewed originated from the left adrenal gland, and those of 5, from the right. In 1 case the enlargement was bilateral. No certain information is available regarding the side in the 2 remaining cases. Malignant tumors were reported in 14 cases, the liver and lungs being the most common sites in which metastases were found. The adjacent kidney was invaded directly in 4 of the cases. The size and weight of the tumors varied widely. They were described as being from the size of a golf ball to that of a man's head. The contralateral adrenal gland was reported as absent in 2, small in 2 and enlarged in 2 cases. Autopsy revealed a colloidal cyst in the pituitary gland of 1 patient; in another patient, hyaline changes were seen in the basophilic cells of the anterior lobe. In 1 patient, atrophy of the thyroid gland and enlargement of the ovaries were found at autopsy. Reduction of the size of the thymus was occasionally reported. Encephalomalacia and internal hydrocephalus were described as cerebral complications.

*Treatment.*—Timely operation is definitely the treatment of choice, and excellent results have been obtained by removal of adrenocortical tumors (Collett,[12] Walters, Wilder and Kepler [26]). However, of the 6 patients who were operated on, only 2 survived the operation. The hypertension and the obesity make the operation difficult. If the tumor

35. Ellis, R. W. B.: Obesity and Hirsutes of Adrenal Origin, Proc. Roy. Soc. Med. **25**:722-724 (March) 1932.

36. Downes, W. A., and Knox, L. C.: Hypernephroma of the Ovary, J. A. M. A. **82**:1315-1317 (April 26) 1924.

37. Gaudier: Tumeur solide de l'ovaire chez une enfant de quatre ans (hypertrophie d'une surrénale du parenchyme ovarien), Bull. et mém. Soc. de chir. de Paris **34**:712-714, 1908.

has become malignant or the contralateral gland is absent or deficient, the prognosis is unfavorable in spite of a successful operation. Two surgical approaches may be employed: the lumbar approach, which necessitates two incisions, one for each side, and is the method of choice, and the transperitoneal approach. Exploration of both glands at operation is advisable, if the patient's condition permits, since with an adrenocortical tumor on one side the contralateral adrenal gland has been found atrophic or absent. The postoperative administration of a physiologic solution of sodium chloride by constant intravenous drip for two to four days is a routine procedure. In conjunction with this procedure, adrenal cortical extract is given intramuscularly for a few days. Signs of adrenal insufficiency should be watched for and treated as they arise. The blood pressure should be determined frequently after operation and the levels of sugar, chloride and urea in the blood determined daily for some time (Kepler, Walters and Piper [38]).

Endocrine treatment has been attempted. Some improvement was noted in Little's [27] patient after treatment with thyroid and ovarian preparations. The patient in a case reported by Pinckney and Main [39] resembled definitely the patient described by us. Although the cause of the pathologic obesity was not established, it is worth noting that improvement followed thyroid treatment in this case. But it must be emphasized again that removal of the tumor will be the treatment of choice as soon as it is diagnosed and whenever it seems feasible. All of the 18 patients included in this review who were not operated on died within six months to four years after the onset of symptoms.

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38. Kepler, E. J.; Walters, W., and Piper, M. C.: Tumors of the Adrenal Cortex: Diagnosis and Treatment and Report of a Case, Proc. Staff Meet., Mayo Clin. **13**:353-361 (June 8) 1938.

39. Pinckney, M. M., and Main, R. J.: Case of Infantile Adiposis Treated with Thyroid, J. A. M. A. **107**:1966-1967 (Dec. 12) 1936.

# News and Comment

## GENERAL NEWS

**Rachford Memorial Lectures.**—Dr. James S. Plant will deliver the Rachford Memorial Lectures in Cincinnati on October 17 and 18. His subjects will be "Inflection Points in the Field of Behavior" and "Negativism, Its Treatment and Its Implications." These lectures will constitute the ninth annual series conducted under the auspices of the Benjamin Knox Rachford Lectureship, which was established by the friends of Dr. Rachford to commemorate his many years of service in the field of pediatrics in Cincinnati.

## UNIVERSITY NEWS

**Western Reserve University.**—Dr. John A. Toomey has been promoted from associate professor of pediatrics in the Western Reserve University School of Medicine to professor of clinical pediatrics and contagious diseases.

## PERSONAL NEWS

**Appointment Announced.**—Dr. Frederick F. Tisdall, associate professor of pediatrics, University of Toronto, and director of the research laboratories of the department of pediatrics and the Hospital for Sick Children, has been appointed consultant in nutrition to the Canadian Active Service Forces, with the acting rank of major.

## DEATHS

On September 2, at the age of 71, Dr. Maud E. S. Abbott died of cerebral hemorrhage. Dr. Abbott's knowledge of congenital cardiac disease was probably not matched elsewhere in the world. Her loss will be felt.

## CORRECTIONS

In the abstract of the article by E. Gedda and K. Kjellberg entitled "Vitamin C Content in Various Swedish Preserves Marketed Under the Name of 'Hagebutten-speisen'" (*Ann. pædiat.* **153**:104 [May] 1939), which appeared in the AMERICAN JOURNAL OF DISEASES OF CHILDREN for August (**60**:388, 1940), the word "hops" which appears in the fifth line from the bottom on page 388 and several times on page 389 should read "hips."

In the abstract of the article by Dr. Norman C. Wetzel entitled "A New Method for Estimating the Physical Development and Nutrition of School Children," which was presented at the meeting of the American Pediatric Society, the report of which appears in the August issue (AM. J. DIS. CHILD. **60**:441, 1940), the average of the mean slopes mentioned in the fifth line on page 458 should be "2.8" instead of "2.3."

In the report of the American Pediatric Society in the September issue (AM. J. DIS. CHILD. **60**:742, 1940), an error occurred in the abstract of the article by Drs. Mildred Weeks Wells and Theodore Stanley Wilder entitled "Epidemiologic Study of Selected Aggregations Breathing Irradiated Air," on pages 759 and 760, in that the word "measles" was inserted in the fourth and sixth lines of the third paragraph, which refers to chickenpox, and in the last sentence of the last paragraph but one on page 760, which refers to mumps.

In the last paragraph of the abstract of the article by Drs. W. F. Wells and Joseph Stokes (page 759), "Marlboro, Mass." should read "Marlboro, N. J."

# Abstracts from Current Literature

## Biochemistry, Bacteriology, and Pathology

M. & B. 693 [Sulfapyridine] and Pneumococci. Ian H. MacLean, Keith B. Rogers and Alexander Fleming, Lancet **1**:562 (March 11) 1939.

The authors describe a method by which the sensitivity of a microbe to sulfapyridine can be tested in vitro. It was found that pneumococci vary enormously in their sensitivity to the drug, and this variation is not associated with the type of pneumococcus but with the individual strain. It is suggested that whenever possible a test should be made. If the organism is very sensitive to the drug, simple treatment will be effective; if it is only moderately sensitive, some increase in immunity will be necessary; if it is insensitive, no good and perhaps harm will result from continued administration of the drug.

Results of experiments on mice support the view that the combined use of vaccines and sulfapyridine is indicated in all cases of pneumonia in man.

Because pneumococci in an infected animal may develop tolerance or "fastness" to the drug it is essential that the initial dose be large and that the immunity be raised to as high a degree as possible by means active or passive, specific or nonspecific, so that the destruction of the bacteria may be complete before tolerance has developed.

Langmann, New York.

Antibacterial Chemotherapeutic Substances. G. Orestano, Med. ital. **20**: 165 (April 30) 1939.

The author reviews the attempts to find useful antibacterial chemotherapeutic substances from the time of Koch to that of Domagk (1935). The contributions of Ehrlich, Mollgaard, Walbum and Morgenroth are discussed. Domagk's work with the "prontosil" compounds is reviewed. The author concludes that the sulfanilamide compounds are useful for streptococcic and gonococcic infections and for several types of pneumococcic infections. Their action on typhoid and paratyphoid infections is still being studied.

The work of Schreus on the treatment of refractory gonorrhea is cited. If patients infected with gonococcus did not respond to the drug, Schreus gave a gonococcus vaccine intravenously and then gave large doses of sulfanilamide. Frequently the refractory patients were cured.

Martoccio, Utica, N. Y.

## Metabolism; Infant Feeding; Milk and Other Foods

Observations on Feeding Infants with Low Fat and Otherwise Modified Evaporated Milk. C. Dixon Fowler, Arch. Pediat. **56**:535 (Aug.) 1939.

Ten children were fed a modified evaporated milk formula. Control observations were made on 10 children fed plain evaporated milk with corn syrup (Karo) added. The advantage observed was the simplicity of preparation.

Orr, Buffalo.

Intravenous Alimentation. Robert Elman and D. O. Weiner, J. A. M. A. **112**:796 (March 4) 1939.

A preparation of hydrolized casein with tryptophane and cysteine added for intravenous use was given in dextrose-Ringer solution to several human beings, including 2 infants. There were no severe reactions. Nutritional edema, when

present, was relieved; the nitrogen balance was restored and the level of plasma proteins elevated. This offers a new field for intravenous alimentation.

HEERSMA, Kalamazoo, Mich.

"GROUPES DE LAIT." D. TIMUS and V. PETRESCU-COMAN, Med. inf., Bucaresti **1**:425 (Nov.-Dec.) 1939.

In studying the *groupes de lait* in 40 nursing women, the authors arrived at the following conclusions:

1. Lactoserum of women contains agglutinins alpha, beta, and alpha and beta.

2. In some cases these agglutinins are absent. They are present in 40 per cent of lactoserums, although according to the researches reported here, the serums of these women contained agglutinins in the proportion of 97.5 per cent.

3. The agglutinins are the same which are recovered from the blood serum. The lactoserum of the women who were of blood groups A and B (their blood serum contained no agglutinins) did not show the presence of agglutinins.

4. When the lactoserum contains the two agglutinins alpha and beta, the phenomenon of agglutination is usually rapid, and most intense with agglutinin beta.

5. The red cells of women are never agglutinated by their own lactoserum.

6. In 25 per cent of the cases the lactoserum of the mother agglutinated the red blood cells of her child, although apparently the latter had a blood group different from that of the mother.

Concerning the troubles produced by the ingestion of lactoserum which agglutinates the blood cells of the child, the authors' researches will be carried further.

In observing the presence of agglutinins in lactoserum one can adopt the classification of milk in the *groupes de lait* by Dujarric de la Rivière, but only in relation to blood groups, not forgetting that what characterizes the blood groups is the difference which exists between the red cells and the presence or absence of isoagglutinins, which constitute, according to Hirsfeld, a secondary phenomenon with respect to the determination of blood groups. FROM AUTHORS' SUMMARY.

## Vitamins; Avitaminoses

THE INTRADERMAL TEST FOR VITAMIN C DETERMINATION. IRVING S. WRIGHT and ELIZABETH MACLENATHEN, J. Lab. & Clin. Med. **24**:806 (May) 1939.

Intradermal injection of 2,6 dichlorphenolindophenol has been suggested as a test for vitamin C deficiency. The authors tried it in a series of cases and found that the results obtained varied so greatly that they do not consider it a reliable index of vitamin C deficiency.

MURRAY, Galveston, Texas.

INFLUENCE OF THE MENSTRUUM ON THE EFFECTIVENESS OF VITAMIN D OBTAINED FROM THE LIVERS OF THE PERCOMORPHI ORDER OF FISH. J. M. LEWIS, J. Pediat. **14**:559 (May) 1939.

It has been previously shown that from the standpoint of equivalent rat unit dosage crystalline vitamin $D_2$ (calciferol) dispersed in the daily ration of milk is several times more effective in preventing or curing infantile rickets than is crystalline vitamin $D_2$ in an oily vehicle. The present study was carried on to determine whether vitamin D from percomorph liver oil is more effective dispersed in the daily ration of milk than prepared in an oily vehicle. This antirachitic preparation is a mixture of oils obtained from fish belonging to the order of the Percomorphi. Throughout the winter months 340 infants, 90 per cent of whom were Negroes, were given comparable amounts of percomorph liver oil either in the form of an emulsion which was dispersed in milk or in the form of an oily

solution which was administered in a half teaspoon of orange juice. Curative tests were also carried out on 21 rachitic infants, all of whom were Negroes. The daily dose of the various preparations ranged from 90 to 200 units. The results of the prophylactic study revealed that while both the emulsion and the oil were effective antirachitic agents, the incidence of rickets was less in the group of infants receiving the emulsion in milk. In the curative test similar results were obtained; the healing response was greater in those infants receiving the preparation in milk than in those receiving the oily solution. Analysis of the data reveals that the emulsion in milk was approximatey twice as effective as the oily preparation at the dosages employed in this investigation.

LOUISE W. RAUH, Cincinnati.

INFANTILE SCURVY: II. STUDIES ON THE CONCENTRATION OF ASCORBIC ACID IN THE TISSUES. T. H. INGALLS, J. Pediat. **14**:593 May) 1939.

This paper presents data on the concentration of ascorbic acid in the livers of 70 infants coming to autopsy. In 27 instances the ascorbic acid content of the adrenal cortex was also determined. The results were correlated with the dietary history and with histologic observations on the rib. At birth the concentration of ascorbic acid in the liver was uniformly high, ranging from 20 to 70 mg. per hundred grams of liver. From birth to 1 month both mean and extreme values were significantly lower, although in only a single instance was the figure less than 10 mg. per hundred grams of liver. Thereafter 18 of 45 infants between the ages of 4 and 26 months showed concentrations of ascorbic acid in the liver below 10 mg. per hundred grams. These concentrations correlated more closely with the dietary intake than with the type or the degree of infection. Patients with histologic evidences of scurvy in the rib showed the lowest concentration of the vitamin in the liver, averaging less than 5 mg. per hundred grams of tissue. Concentrations of ascorbic acid in the adrenal cortex varied between 3 and 158 mg. per hundred grams of tissue and showed some correlation with dietary intake, although they did not closely parallel the ascorbic acid concentration in the liver. The explanation may be that the liver reflects more quickly a diminution or an increase in the ascorbic acid reserve.

RAUH, Cincinnati.

VITAMIN A REQUIREMENTS IN INFANCY AS DETERMINED BY DARK ADAPTATION. J. M. LEWIS and C. HAIG, J. Pediat. **15**:812 (Dec.) 1939.

A method to determine the minimum threshold of the perception of light after complete dark adaptation in infants is described. The method was used to test a series of infants, and the results obtained showed that infants on a low vitamin A diet, receiving as little as 135 to 200 units of vitamin A daily, have as low a threshold for vision in the dark as infants receiving an average diet complemented by 17,000 units of vitamin A. Those infants receiving only 135 to 200 units of vitamin A daily gained weight as well and were no more susceptible to infections than those receiving 17,000 units of vitamin A. Since the average diet contains approximately twelve times as many units of vitamin A as were contained in the low vitamin A diet (135 to 200 units), there is a large margin of safety in the infants' diet with respect to its vitamin A content. It seems, therefore, unnecessary to supplement the average diet of infants with special preparations which contain vitamin A. Three infants, 2 of whom had eczema, received as a substitute for milk, a preparation containing soy bean, starch and olive oil. This product is almost devoid of vitamin A. In three to four weeks these infants had poor dark adaptation. The addition of 120 units of vitamin A in the form of cod liver oil resulted in a return of dark adaptation to normal in 2 of these infants. A single dose of vitamin A, 30,000 to 50,000 units, given to 2 infants in whom high thresholds had developed on this diet caused the dark adaptation to return to normal in forty minutes in one infant and in sixty-five minutes in the other.

RAUH, Cincinnati.

PLASMA ASCORBIC ACID OF INFANTS AND CHILDREN. C. E. SNELLING, J. Pediat. **15**:824 (Dec.) 1939.

The ascorbic acid of the blood plasma was measured for 158 infants and 77 older children shortly after admission to the hospital. Thirty-one breast-fed infants had an average of 0.76 mg. per hundred cubic centimeters; 127 artificially fed infants, an average of 0.23 mg. Seventy-nine of the artificially fed infants were receiving 2 ounces (60 cc.) or more of orange juice daily and had an average of 0.30 mg. of ascorbic acid per hundred cubic centimeters. Forty-eight of the artificially fed infants with little or no orange juice supplement had an average of 0.12 mg. per hundred cubic centimeters. None of these infants had clinical signs of scurvy. Seventy-seven children 2 to 14 years of age had an average of 0.75 mg. per hundred cubic centimeters. Ascorbic acid given by mouth to 39 infants with low values of plasma ascorbic acid caused a definite rise in the plasma level in 15 of 24 patients after one dose and in 8 of 11 patients after it had been administered for a period of two to three days. Infants with scurvy when treated with ascorbic acid required treatment over a far longer period before any increase in plasma ascorbic acid resulted. Snelling believes that low values by themselves do not give a picture of the general ascorbic acid nutrition of the child and cannot be used as a standard for the diagnosis of scurvy.

RAUH, Cincinnati.

ACTION OF VITAMIN $B_1$ ON THE EXCRETION OF CREATINE. B. VASILE and F. PECORELLA, Pediatria **47**:475 (June) 1939.

Vasile and Pecorella gave 10 mg. of vitamin B per day to each of 4 children on a creatine-free diet. Their ages were from 6 to 9 years. The vitamin was given subcutaneously daily for an average of ten days. The volume of the urine, the total creatinine, the preformed creatinine, the creatine and the creatinine coefficient were determined in each case. During the administration of the vitamin B there was reduction, sometimes disappearance, of the creatine. After discontinuing the treatment there was a gradual return of the creatine to its original level. The probable cause for this reduction in creatine is reviewed.

MARTOCCIO, Utica, N. Y.

VITAMIN C CONTENT IN WELL AND SICK CHILDREN. L. F. MEYER and P. ROBINSON, Ann. pædiat. **152**:283 (Feb.) 1939.

In order to form a clear opinion of the vitamin C balance of the organism it is necessary to determine the twenty-four hour excretion of ascorbic acid in the urine and the amount present in the blood. At the same time ascorbic acid should be given experimentally in order to ascertain the requirements of the body.

The excretion is directly dependent on the intake. The majority of the population excretes minimum quantities during the summer, but during the winter the excretion rises considerably on account of the consumption of cheap citrus fruit rich in vitamin C.

In the hospital the infant needs about 20 mg. per day. The toddler requires 30 to 45 mg., according to the season.

An exact study of the vitamin C balance which takes into account the experiments with increased intake of ascorbic acid demonstrates that during the summer the poorer section of the population lacks vitamin C to a considerable degree. The necessary dose is about 500 mg.

Meyer and Robinson have not been able to show with present methods that children require more vitamin C during a febrile period.

It is possible that in severe diarrhea ascorbic acid given by mouth may be disposed of in an abnormal manner inside the intestine. When absorbed into the blood it may be diminished or altered. It will, however, exert its full beneficial effect if given parenterally.

In about half the cases of severe toxicosis the cells were unable to absorb ascorbic acid (*refus cellulaire*). Children with *refus cellulaire* had a bad prognosis; those without *refus cellulaire* had a far better prognosis.

FROM AUTHORS' SUMMARY.

## Hygiene; Growth and Nutrition; Public Health

HEALTH OF THE NATION. Pub. Health Rep. **54**:2269 (Dec. 29) 1939.

Only 22,564 cases of diphtheria were reported for forty-nine weeks of 1939 as compared with 28,034 for 1938. Similar encouraging results are noted in regard to all the contagious diseases. It might also be noted that the death rate for measles was only about one tenth of that in 1900. There is apparently an increase in influenza at present. The report emphasizes the harmfulness of public opinion regarding such diseases as poliomyelitis while the public remains indifferent to other conditions. Roughly 80 persons die of tuberculosis for every one that dies of poliomyelitis. There are as many deaths from tuberculosis each year as there have been cases of poliomyelitis in the past ten years.

The average death rate for the week ending Dec. 4 was 11.3 per thousand, compared with 11.5 for the same period in 1938.

SANFORD, Chicago.

DISABLING CHILDHOOD DISEASES OBSERVED IN NATIONAL HEALTH SURVEY. D. F. HOLLAND, Pub. Health Rep. **55**:135 (Jan. 26) 1940.

This represents a canvass of 518,767 white children under 15 years of age in 83 urban communities by the United States Public Health Service from 1935 to 1936. Disabling illnesses occur more frequently in the group under 15 years of age than in any other age group, but their duration in that group is shorter. Four in every five of the disabling illnesses among these children were acute communicable diseases or diseases of the respiratory tract. These conditions account for over one half of the disability of the average child in the twelve month period. Permanent orthopedic impairments incapacitated 12 in every 10,000 children and were found in 49.5 of every 10,0000. Congenital defects, accidents and poliomyelitis were the most frequent causes.

SANFORD, Chicago.

INFLUENCE OF VARIOUS FACTORS ON THE SOMATIC DEVELOPMENT OF THE FETUS AND THE NEWBORN. A. PICCIOLI, Lattante **10**:395 (Oct.) 1939.

A study of weight and height was made on 3,343 infants born of 3,271 mothers.

The tallest and heaviest infants were those born to mothers who were between the ages of 26 and 35, while the shortest and lightest were those born to mothers who were under 20 and over 46 years of age.

The weight and height of infants of working mothers were in general lower than those of infants whose mothers remained in the home.

The legitimate children were in general larger than the illegitimate.

The weight and height of the newborn infants bore a direct relation to the duration of the pregnancy. Thus, children born after forty-two weeks' gestation averaged 240 Gm. heavier than children born at term.

The size of children of the second to the fifth pregnancy was greater than that of children of the first or of pregnancies subsequent to the sixth.

The longer time during pregnancy the mothers had been under medical supervision the heavier were their offspring.

Males in general were larger than females and twins smaller than single babies.

The children born between October and March were larger than those born between April and September.

HIGGINS, Boston.

SOME NEW LEGISLATION BENEFITING CHILDREN. M. BERGAMINI, Lattante **10**:419 (Oct.) 1939.

Under the new civil code of Italy the laws regarding adoption of children are clarified and render better protection for the child. A new term is used indicating affiliation (*affigliazione*), or bringing the child into the family, where the parents assume definite familial as well as legal responsibilities of adoption.

HIGGINS, Boston.

RESOURCES FOR INTER-AMERICAN CHILD WELFARE WORK. K. F. LENROOT, Bol. Inst. internac. am. de protec. a la infancia **13**:229 (Oct.) 1939.

It is apparent that the resources now available through international and inter-American organizations and the possibility of coordinating and expanding these resources should receive careful study. It is proposed, therefore, that steps be taken by the Eighth Pan-American Child Congress to provide for consultation on the part of the International American Institute for the Protection of Childhood, the Pan-American Union, the Pan-American Sanitary Bureau, and such experts as they may desire to call into consultation, with reference to the following points:

1. A review of the organization, methods and results of the Pan-American child congresses.

2. A study of the facilities now provided or that might be developed by the International American Institute for the Protection of Childhood, the Pan-American Union, the Pan-American Sanitary Bureau and other organizations.

3. The relationship of the child congresses and the permanent inter-American organizations carrying on child welfare work to Pan-American sanitary conferences and other conferences dealing with public health or social welfare and to the international conferences of American states.

4. Recommendations concerning the subjects studied and the methods of coordinating the work of the various organizations considered.

5. A report of progress to the Ninth Pan-American Child Congress and the Ninth International Conference of American states.

FROM AUTHOR'S SUMMARY.

FORM AND FUNCTION IN CHILDREN. I AND II. B. P. B. PLANTENGA and S. M. C. VAN VEEN, Nederl. tijdschr. v. geneesk. **83**:3318 and 3326 (July 1) 1939.

In part I the authors consider the development of form in the child. The importance of the constitutional factor is brought forward. They describe the types of Kretschner as observed in children, with appreciation of the various factors interfering with the constitutional type, among which the phase of development and cerebral, endocrine and conditional factors are discussed in detail.

In part II the question as to existence of a correlation between form and function in infants and very young children is answered in the affirmative. Children with dysharmonic reaction to animal fats have a pyknic, those reacting dysharmonically to animal proteins, a leptosomic, stature. Similar correlations have been found with the athletic type. The connections between body build and nutrition and between eczema and the course taken by infections are considered in detail.

VAN CREVELD, Amsterdam, Netherlands.

THE ADMISSIBLE QUANTITY OF LEAD IN DRINKING WATER, THE DAILY INTAKE OF LEAD BY THE NORMAL MAN AND THE QUESTION OF CHRONIC LEAD INTOXICATION. J. F. REITH and L. W. VAN ESVELD, Nederl. tijdschr. v. geneesk. **83**:5632 (Dec. 2) 1939.

A discussion of the question as to what quantity of lead in the drinking water should be considered admissible leads to the conclusion that the problem must be seen in connection with the total daily intake of lead. Sometimes the

lead from the drinking water takes the main place, and sometimes it is of little or no importance. In view of the fact that one is still imperfectly informed as to the quantity of lead that must be held to be injurious for the human organism, one must aim at lessening the lead content of all kinds of possible sources of lead (diet, drinking water, street dust) with which man is in contact. For drinking water the limit advised is 0.3 mg. per liter after eight hours of stagnation in the conduct pipe. New pipes can be admitted to give off two to three times this quantity during the first four months. VAN CREVELD, Amsterdam, Netherlands.

## Newborn

BOWEL OBSTRUCTION IN THE NEW BORN. EDWIN M. MILLER, Ann. Surg. **110**: 587 (Oct.) 1939.

The frequency of congenital obstruction of the bowel in the newborn, excepting imperforate anus, is difficult to estimate. Over 500 cases have been recorded, and most authors feel that 1 in 20,000 infants at birth are thus affected.

It is probable that the great majority of obstructions are due to errors or defects in embryonic development. In general, two main types of pathologic condition are recognized: (1) the intrinsic, consisting usually of a complete gap or interruption in the continuity of the bowel, and (2) the extrinsic, caused by abnormal folds of peritoneum, adhesions left by fetal peritonitis, direct pressure from overlying large vessels or faulty rotation of the cecum or ascending colon.

Early recognition of an obstruction in the newborn is essential if successful results are to be expected. In the differential diagnosis of pylorospasm or congenital pyloric stenosis, especially in the absence of a palpable tumor, with early vomiting (after the first nursing or the first few days of life) one must always consider the possibility of partial or complete obstruction in the first portion of the duodenum. The presence of bile in the vomitus, coupled with visible peristaltic waves in the epigastrium, flatness of the lower quadrants of the abdomen and rapid dehydration is almost unmistakable evidence of an obstruction of the duodenum below the ampulla of Vater. Persistent vomiting, when the vomitus soon becomes fetid and brown and is associated with general abdominal distention and obstipation, can only mean partial or complete obstruction lower down. In any case in which doubt exists, it is wise to use roentgen examination.

The prognosis depends on the location of the obstruction. It is very bad if this is in the jejunum or the ileum and less bad if it is in the duodenum. If the obstruction is due to abnormal bands or adhesions the prognosis is much more favorable.

The author reviews 36 cases. BANTIN, Omaha.

EPIDEMIC DIARRHEA OF THE NEWBORN. ROY P. FORBES and FRANK B. OLSEN, Arch. Pediat. **56**:250 (April) 1939.

Eleven cases are reported. Five of the patients died. ORR, Buffalo.

FACTORS INFLUENCING PLASMA PROTHROMBIN IN THE NEWBORN INFANT: I. PREMATURITY AND VITAMIN K. L. M. HELLMAN and LANDRUM B. SHETTLES, Bull. Johns Hopkins Hosp. **65**:138 (July) 1939.

Working from the observations of Brinkhous and his associates on the variation of the plasma prothrombin level of the newborn full term normal infant as compared to that of the normal adult, the authors found that the average value for plasma prothrombin for 8 mothers was 126.9 units and for 9 premature infants was 8.3 units. For 19 full term newborn infants the level was 22.2 units. Studies indicate that low infant prothrombin levels can be raised by feeding vitamin K to the mother before delivery or to the infant after birth.

LYTTLE, New York.

CURVES OF SLEEP IN NEWBORN INFANTS. I. F. WAGNER, J. Genet. Psychol. **55**:59 (Sept.) 1939.

The curves of depth of sleep in the newborn are highly variable from infant to infant and from day to day in the same infant. There is a tendency for the variability in the individual curve to decrease with age. The infants were awake 40.3 per cent of the time and sound asleep only 12.7 per cent of the time. Such activities as yawning, sneezing, hiccuping, crying and audible defecation were most likely to occur during waking stages and never during stages of deep sleep.

WEINFELD, Highland Park, Ill.

WHITE BLOOD CELLS OF THE NEWBORN INFANT. F. RASI and O. CELLEGHIN, Riv. di clin. pediat. **37**:711 (Aug.) 1939.

Studies of the blood were made one hour, twelve hours, twenty-four hours, forty-eight hours and five days after the nontraumatic delivery of 15 infants.

In each case the number of red cells and the percentage of hemoglobin increased up to twenty-four hours and then fell. The average red cell count at birth was 5,600,000 per cubic millimeter; at twenty-four hours, 6,325,000, and at five days, 4,920,000. In each case the number of white cells was above normal at birth (average 14,170 per cubic millimeter) and had fallen to normal by the fifth day (average 9,890). In 11 cases the white cell count paralleled the rise in the red cell count for twenty-four hours; in the other 4 cases the fall was gradual to the fifth day. The increased white cells were mainly polymorphonuclear cells (71 per cent). The Arneth classification showed a shift to the right. Immature cells both of the white and of the red series were found in the smears at birth.

HIGGINS, Boston.

INTRACRANIAL HEMORRHAGE IN PREMATURE AND NEWBORN CHILDREN. HERBERT KOCH, Ztschr. f. Geburtsh. u. Gynäk. **119**:52 (May) 1939.

Reviewing the autopsy material of past years in which only macroscopic findings were recorded and comparing it with recent material in which a thorough microscopic examination of the brain has been done, the author finds that according to his series the incidence of hemorrhage into the brain substance proper is much greater than the older literature indicates. Intracranial hemorrhage is discussed in relation to localization, importance as a cause of death and possible causation by asphyxia.

No attempt is made to correlate the observations with the clinical course of labor and delivery.

ADAIR and POTTER, Chicago.

INTRACARDIAC USE OF EPINEPHRINE IN ASPHYXIA PALLIDA NEONATORUM. JOSEPH OSTRCIL JR., Časop. lék. česk. **76**:456 (April 16) 1937.

The author reviews the literature on intracardiac injections of epinephrine in cases of asphyxia pallida neonatorum and favors the method of Vogt, who recommended injection of the substance into the left upper angle of the fourth intercostal space and the sternum. Of 20 patients treated, 3 recovered, 2 permanently and 1 for thirty hours. The dose used was 0.3 to 0.5 mg. of epinephrine with 1 cc. of lobeline for stimulation of the respiratory center.

STULIK, Chicago.

A CASE OF WINCKEL'S DISEASE WITH RECOVERY. P. H. F. DOP, Acta pædiat. **23**:397, 1939.

Cyanosis afebrilis icterica perniciosa cum haemoglobinuria, or Winckel's disease, is a malady of newborn infants that has a tendency to occur in epidemics but sometimes appears in isolated instances. The cause is unknown, although various poisons such as phenol, potassium chlorate and aniline dyes have been thought to

be responsible; its epidemic character has frequently encouraged the search for an infectious agent. The important pathologic feature is widespread hemorrhagic infiltration of all the organs of the body. The disease is characterized by the sudden appearance of icterus, cyanosis and brown urine. The urinary pigment was formerly thought to be hemoglobin but is now known to be methemoglobin. Methemoglobinemia is also present. Spectroscopic examination reveals this substance in both the erythrocytes and the plasma. The onset occurs usually about the third or fourth day of life but may be delayed to the end of the second week. The course is fulminating, and death usually occurs within forty-eight hours. Transfusion appears to be of some benefit. The mortality is about 85 per cent. The best review of the literature is that of Polayes and Kramer (*J. Pediat.* **2**:482 [April] 1933).

Dop reports on a 14 day old infant who exhibited all of the classic manifestations of the disease. He ascribes the recovery to intramuscular injections of whole blood. Oxygen also was used.

McCUNE, New York.

PHYSIOLOGIC ENLARGEMENT OF THE SPLEEN IN NEWBORN INFANTS. Y. ÅKERRÉN, Acta pædiat. **24**:23, 1939.

Systematic daily examination of 144 newborn infants revealed that the spleen enlarged to the point of becoming palpable on at least one occasion in 77 per cent of the cases. The viscus was most commonly palpable between the second and fourth days of life. The transient enlargement is ascribed to engorgement with blood.

McCUNE, New York.

ICTERUS GRAVIS NEONATORUM AND ANAEMIA NEONATORUM. E. APPELBERG-ULFSPARRE, Acta pædiat. **24**:30, 1939.

Four cases of icterus gravis and 3 of anaemia neonatorum are reported. Among others, the following points are made: 1. Erythroblastosis is a transient phenomenon both in icterus gravis and in anaemia neonatorum. 2. The prognosis for both is independent of the degree of erythroblastosis.

McCUNE, New York.

## Acute Contagious Diseases

ACTIVE IMMUNIZATION AGAINST WHOOPING COUGH. N. SILVERTHORNE, Canad. M. A. J. **41**:263 (Sept.) 1939.

The first part of this report deals with the results of the use of a fresh vaccine, reported according to the method of Silverthorne and Fraser. The total dose over a four week period was approximately 120,000 million bacilli. Two hundred and eighty-eight (288) controls and 1,007 vaccinated children were followed. Of 52 controls coming in contact with children who had whooping cough, 82 per cent acquired the disease; of 97 vaccinated children similarly exposed, 10 per cent acquired the disease.

MOORE, Omaha.

POTASSIUM CHLORATE IN THE TREATMENT OF POLIOMYELITIS. J. SAUCIER and W. STEWART, Canad. M. A. J. **42**:19 (Jan.) 1940.

Experiments were done to repeat as exactly as possible work reported by Contat, Arthus, Spycher and Debat. The latter reported evidence of a specific protective action of potassium chlorate in experimental poliomyelitis in monkeys.

Potassium chlorate, given orally in doses of 10 to 20 centigrams per kilogram of body weight in twenty-four hours, failed to protect or influence favorably the course of the disease in monkeys (Macacus rhesus) inoculated with several strains of poliomyelitis.

MOORE, Omaha.

After-Treatment of Poliomyelitis. K. G. Hannson, J. A. M. A. **113**:32 (July 1) 1939.

Hannson discusses the principles underlying the after-care in cases of poliomyelitis. Recovery depends on the type of pathologic change in the spinal cord, i. e., on whether there is temporary inflammatory pressure, anoxemia or infection of the cells of the anterior horn, or permanent injury and death. Treatment is directed toward assisting the recovery of the damaged tissues and toward sparing and preserving the muscle and skeletal structures. In Hannson's series of 54 cases treatment consisted in immobilization in the acute stage and underwater exercises immediately after tenderness had disappeared. The percentage of muscle recovery was similar to that with use of heat, massage, electrical stimulation and muscle reeducation in a comparable series reported by Harry. Treatment begun early was twice as effective as that begun late. Hannson feels that physical therapy in a pool, when it is possible, has distinct advantages in providing heat, security and pleasure and eliminating overexertion, muscle imbalance and the harmful effects of gravity.

Heersma, Kalamazoo, Mich.

H. Pertussis Vaccines: The Effect of Washing and the Use of Mouse Protection Tests. J. J. Miller Jr. and R. J. Silverberg, J. Infect. Dis. **65**:16 (July-Aug.) 1939.

Washing Haemophilus pertussis phase I vaccine with either an 0.85 per cent solution of sodium chloride or distilled water removed similar amounts of soluble protein. This protein in both solvents was specifically precipitable with H. pertussis antiserum and was antigenic for rabbits. There was no evidence indicating that distilled water denatured the specific protein in solution.

Comparative mouse protection tests were done with unwashed phase I vaccine, with vaccine washed once in an 85 per cent solution of sodium chloride and with vaccine washed once in distilled water. When vaccinated and control mice were infected intranasally, evidence of protection by unwashed vaccine was suggested. When vaccinated and control animals were infected intraperitoneally with a suspension of H. pertussis in 5 per cent hog's gastric mucin, definite evidence of protection with all three vaccines was obtained.

These observations on washings and on washed vaccines indicate that washing with distilled water has no more effect on H. pertussis phase I vaccines than does washing with an 85 per cent solution of sodium chloride. It would seem, however, that washing is unnecessary and that it removes a small amount of antigen. These observations fail to explain the lack of protection with vaccine washed with distilled water as reported by Doull, Shibley and McClelland.

Of the various technics used in mouse protection tests, intraperitoneal injection of a massive dose of H. pertussis in 5 per cent hog's gastric mucin was found most reliable in producing fatal infection in unvaccinated animals.

Toomey, Cleveland. [From Authors' Summary.]

Relationship Between Humoral and Tissue Immunity in Experimental Poliomyelitis. E. H. Lennette and N. P. Hudson, J. Infect. Dis. **65**:78 (July-Aug.) 1939.

The authors describe three experiments:

1. Fifteen healthy rhesus monkeys were each given an injection of poliomyelitis virus by the vascular route. In 7 of them the neutralizing property of the serum developed; 13 succumbed to an acute attack of poliomyelitis after an intracerebral inoculation of the virus; 2 died of intercurrent infection.

2. Three monkeys were passively immunized by the intravenous route, and these showed no signs of infection following an intravenous injection of virus coincident with an intracerebral injection of starch solution to damage the blood–central nervous system barrier.

3. Twenty monkeys were given an intravenous injection of virus. The neutralizing property developed in the serum of 9; it was absent from the serum of 9; the serum of the remaining 2 was not tested. When these 20 monkeys were given an intravenous injection of virus coincidentally with an intracerebral injection of starch solution, 8 of those with neutralizing serum, 2 of those whose serum was negative and the 2 whose serum was not tested for the neutralizing property resisted infection. The 11 surviving monkeys (1 had died of an intercurrent infection) each received an intracerebral injection of the virus, and 7 suffered acute attacks.

In these experiments about half the animals that succumbed to virus injected intracerebrally had acquired serum antibodies against the virus of poliomyelitis.

The methods of active and passive immunization employed were effective in protecting about three fifths of the monkeys against intravenous injections of virus plus intracerebral injections of starch. Among the 12 animals having circulating antibodies, 11 resisted this type of experimental inoculation. Virus injected vascularly was apparently neutralized in the blood stream.

In attempting to analyze the results of these experiments, it became evident that the outcome was directly related to whether the experimentation was directed to the non-neural parts of the body or to the central nervous system. Each part displayed its own role in immunity of the body, and experiments designed to associate the immunity of the non-nervous and the nervous tissues were not successful. Apparently, the insulatory mechanism of the central nervous system is significant in the distinction between the so-called humoral and tissue immunity in experimental poliomyelitis.

TOOMEY, Cleveland.

INTRANEURAL INJECTIONS OF SERUM AS A BARRIER TO MIGRATION OF VIRUS IN EXPERIMENTAL POLIOMYELITIS. J. A. HARRISON and O. C. WOOLPERT, J. Infect. Dis. **65**:214 (Sept.-Oct.) 1939.

Seven monkeys were given intracerebral injections of poliomyelitis virus and subsequently intraspinal injections of virus-neutralizing serum. All succumbed to typical poliomyelitis, with complete flaccid paralysis of all extremities. The pathologic changes noted in histologic sections of the lumbar part of the cord were those of poliomyelitis and were no less marked than the similar changes observed in the cervical part of the cord.

In 8 monkeys virus was injected into the sciatic nerve, accompanied by a proximal injection of immune serum. In 1 of these animals typical poliomyelitis developed. Eleven other inoculations of virus alone into sciatic nerves failed to produce the disease.

The observers conclude that under the conditions of the experiment poliomyelitis immune serum introduced into the assumed neural pathway of the poliomyelitis virus did not halt the progress of the virus or modify the course of the experimental disease.

TOOMEY, Cleveland.

VALUE OF CONVALESCENT SCARLET FEVER, MEASLES AND MUMPS SERUMS IN PROPHYLAXIS AND THERAPY. W. THALHIMER, M. Clin. North America **23**: 613 (May) 1939.

An extensive experience in many parts of the world has demonstrated the value of measles convalescent serum in preventing or modifying the disease. Since the ideal method of active immunization is not available, passive immunization should be employed to limit the hazards of the disease, particularly in young and debilitated children. Up to the age of 2 years and perhaps 5 years, an attempt at complete protection should be made. For children 5 years of age and under, an intramuscular dose of 5 cc. of serum will usually prevent the disease if given up to the fifth day of exposure. From the sixth to the eighth day a slightly larger dose is necessary. Later than the eighth day the results are not dependable. After the age of 5 years the early dose should be 1 cc. for

each year of age. After the sixth day, and in the case of debilitated children or those suffering from other diseases, one and one-half to two times the standard dose should be given. This larger dose should also be given to children in institutions and those living in crowded and unhygienic surroundings. The serum does not cause sensitization even when it is given repeatedly at ten day intervals. Opinions conflict as to its value in the preeruptive and eruptive stages of the disease, but sufficient evidence of its value in these conditions has been presented to merit further studies.

The value of convalescent scarlet fever serum in the prophylaxis and treatment of this disease is now definitely established. A prophylactic dose of 20 cc. of serum given intramuscularly will reduce the expected incidence of 10 to 15 per cent in exposed children to about 1 per cent. For treatment the serum should always be given intravenously, and there need be no fear of anaphylactic shock, severe reactions or sensitization to subsequent injections. The suggested doses are 20 cc. for children up to 5 years of age, 40 cc. for those from 5 to 10 years, 60 cc. for those between 10 and 15 years, and 80 to 100 cc. for large adolescents and adults. Usually one dose is sufficient, but more may be given. In uncomplicated cases one may expect good results even when the serum is given as late as the sixth day. When complications exist or are likely, it is advised to give three standard doses at eight hour intervals.

The serum has also proved of value in severe hemolytic streptococcic infections other than scarlet fever.

Mumps convalescent serum appears to be of value as a prophylactic agent when given in doses equal to those recommended for scarlet fever serum. It is also reported to be of value when given in doses of 40 cc. by the intravenous route.

EUGENE H. SMITH, Ogden, Utah.

CONVALESCENT SERUM IN THE PREVENTION AND TREATMENT OF COMMON CONTAGIOUS DISEASES IN CHILDHOOD. R. T. LUCAS, New Orleans M. & S. J. **92**:289 (Dec.) 1939.

Lucas presents a brief review of the recent literature on the use of human convalescent serum in the treatment of measles, scarlet fever, whooping cough, mumps, chickenpox and poliomyelitis.

BERKLEY, Los Angeles.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **54**:1911 (Oct. 27) 1939.

For the period of Sept. 10 to Oct. 7, 1939, 1,873 cases of poliomyelitis were reported. The incidence of the disease declined later in the period. Every region of the country reported an increase in incidence except the east south central. There were 125 cases of smallpox, of which the highest incidence was confined to the states in the central and western regions. The incidence of diphtheria, influenza, measles, meningitis, scarlet fever and typhoid was below the median average. During this period of four weeks the average mortality rate from all causes in large cities was 10.1 per thousand inhabitants, which is exactly the same as it was for the preceding five years.

SANFORD, Chicago.

RECOVERY OF THE VIRUS OF POLIOMYELITIS FROM STOOLS OF HEALTHY CONTACTS IN AN INSTITUTIONAL OUTBREAK. S. D. KRAMER, Pub. Health Rep. **54**:1914 (Oct. 27) 1939.

In a separate wing of a small institution comprising 20 infants and children of preschool age, from 2 months to 5 years, 5 children contracted poliomyelitis, with fatal results in 1 child and nonparalytic results in 4 children. Three additional children showed evidence of fever of from twenty-four to forty-eight hours' duration. The clinical observation of all of the children in the institution was excellent and included the routine recording of temperature twice daily.

The virus of poliomyelitis was recovered from the stools of 3 of the 12 remaining healthy children, from contacts of children having the disease and from 2 of the 3 children who showed evidence of fever but for whom a diagnosis of poliomyelitis was not established. Thus, including the 5 children with clinical infections, whose stools, however, were not examined for virus, 10 of the 20 children harbored the virus of poliomyelitis at some time in the thirty day period of Aug. 1 to Aug. 30, 1939. SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **54**:2077 (Nov. 24) 1939.

In the period from Oct. 8 to Nov. 4, 1939, the cases of poliomyelitis dropped to 1,163. This was about one and one-fourth times the average of the last five years. One peculiarity of the disease was that it was not confined to any one area but was spread throughout the country. The cases of influenza, as was to be expected, increased to 3,361, which is about 25 per cent above the average. This was in the south Atlantic, west south central and mountain regions. The cases of diphtheria, measles, meningitis, scarlet fever, smallpox and typhoid were below the seasonal incidence. The average mortality from all causes was 10.4 per thousand, which is below the normal. SANFORD, Chicago.

HUMAN SERUM AS A STABILIZER OF SCARLET FEVER STREPTOCOCCUS TOXIN DILUTED FOR THE DICK TEST. M. V. VELDEE, Pub. Health Rep. **54**:2131 (Dec. 1) 1939.

This study indicated that human serum added in the concentration of 1:500 to the 10 per cent phosphate buffer in physiologic solution of sodium chloride commonly used in this country in preparation of the Dick test toxin effectually protects the skin-reacting factor against deterioration for an interval of time considerably over the present allowable dating period, within a temperature range of 5 to 37 C. and a $p_H$ range of 6.6 to 7.4. There was no evidence that this serum influences the skin reactions in man or rabbit. SANFORD, Chicago.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **54**:2239 (Dec. 22) 1939.

In the period from Nov. 5 to Dec. 2, 1939, there was an increase in poliomyelitis over the corresponding period in 1938 but a drop from the preceding period. The incidence is the highest since 1931 and is remarkable on account of the length of time that it has been high. The incidence of influenza was also 1.5 times higher than in the corresponding period in 1938. Other diseases were under the median prevalence. The average mortality from all causes was 10.9 per thousand, the lowest in eight years. SANFORD, Chicago.

PASSIVE IMMUNITY IN EXPERIMENTAL PERTUSSIS. E. A. NORTH, E. V. KEOGH, G. ANDERSON and S. WILLIAMS, Australian J. Exper. Biol. & M. Sc. **17**: 275 (Sept.) 1939.

The authors used the reduction of mortality in mice given lethal doses of Haemophilus pertussis (phase I) intranasally as the criterion of the protective power of serum given intraperitoneally in the amount of 0.25 to 0.30 cc. four (occasionally eighteen) hours before the infecting dose. A protective antibody was shown to be present in the serum of children convalescent from whooping cough, of children immunized with H. pertussis (phase I), of some adults who had come in contact with patients with whooping cough and of rabbits immunized with living cultures of H. pertussis, both virulent (phase I) and avirulent (phase III) strains. It was not detectable in pooled serum of healthy adults or in the serum of children who had not had whooping cough and who had not been

immunized. Inasmuch as the antibody-containing serum did not protect mice against a lethal dose of pertussis endotoxin or exert any neutralizing effect on the necrosis following intradermal injection of endotoxin in rabbits, it is assumed that the protective antibody is antibacterial in its action. There was no correlation between the phase I agglutinin titer and the protective potency of the serum. The significance of these findings is discussed, and it is concluded that this antibody plays an important part in the resistance to whooping cough of children who have recovered from the disease or who have been prophylactically immunized.

CEREBROSPINAL FLUID IN ANTERIOR POLIOMYELITIS. J. C. DRURY and A. F. SLADDEN, Brit. M. J. **2**:557 (Sept. 9) 1939.

This is an account of a study of the spinal fluid in an outbreak of anterior poliomyelitis. The study is summarized in the following conclusions:

"Detailed analysis of spinal fluid is a valuable adjunct in the detection and diagnosis of poliomyelitis and polioencephalitis.

"The finding of a completely normal fluid practically excludes a diagnosis of this disease.

"Slight pleocytosis is a constant feature and a few polymorphs are commonly present in the early stages.

"Slight protein increase is usual and develops with progress of the disease.

"Globulin, if only a trace, is always found. The Lange gold curve often affords useful corroborative evidence."

ROYSTER, University, Va.

SULPHANILAMIDE IN THE TREATMENT OF SCARLET FEVER. E. C. BENN, Brit. M. J. **2**:644 (Sept. 23) 1939.

An investigation has been made by Benn along the line indicated in the title. There was a control series. Antiscarlatinal serum was given to those patients in both groups who were thought to require it, irrespective of the giving of sulfanilamide. The author had realized that sulfanilamide would have little or no effect in the acute febrile stage of scarlet fever except the septic type. In cases of the septic type it probably is effective in reducing the incidence of complications. The study was limited to children under the age of 10 years. The drug apparently had a definite value in cases in which some septic element was present, and complications apparently were fewer in the drug-treated series.

ROYSTER, University, Va.

DOES POLIOMYELITIS AFFECT INTELLECTUAL CAPACITY? AN INVESTIGATION ON NINETY-EIGHT CASES. R. G. GORDON, J. A. F. ROBERTS and R. GRIFFITHS, Brit. M. J. **2**:803 (Oct. 21) 1939.

Tests of the intellectuality of patients suffering from poliomyelitis or the results of it were made on the basis of the Stanford-Binet scale. It was found that neither at the time of the attack nor subsequently was the intellectual level affected. It must be remembered that many affected children are kept from school and other educational advantages for long periods of time, and unless they are taught and their scholarship kept up they will show a retardation not in mental capacity but in knowledge. Also emotional reactions are apt to develop in these children, with serious maladjustments of personality. Thus there may be educational backwardness simulating true mental retardation.

ROYSTER, University, Va.

DIPHTHERIA: A SUGGESTED EXPLANATION OF THE RELATIVE CHANGE IN AGE INCIDENCE. E. A. CHEESEMAN, W. J. MARTIN and W. T. RUSSELL, J. Hyg. **39**:181 (March) 1939.

The death rate from diphtheria in England and Wales has decreased rapidly in children of preschool age but less rapidly in those from 5 to 9 years of age. Whereas it was 1,565 to 4,390 per million in the two years from 1900 to

1902, it was 497 to 1,070 in the two years from 1930 to 1932. The rate of decrease for children over 5 years shows about half this drop. A decline in the average size of the families in the lower social grades probably explains the relative change in the distribution by age, rather than a change in the type of organism causing the disease.

Because the families are becoming smaller, the housing conditions have improved, and the children born in these communities have conditions more like the higher social classes. In proportion, more children reach school as a "virgin" population and become infected in the environment of the school classroom.

JANNEY, Wauwatosa, Wis.

A STUDY OF HETEROLOGOUS ANTIBODIES IN THE SERUM OF POLIOMYELITIS PATIENTS. F. M. BURNET, M. FREEMAN, A. V. JACKSON and D. LUSH, M. J. Australia **2**:198 (Aug. 5) 1939.

The examination of 70 specimens of serum from patients with poliomyelitis for their content of heterologous antibodies against the viruses of herpes simplex and swine influenza and for diphtheria and staphylococcic antitoxins provided a number of points of general epidemiologic interest. No evidence was found that any of the heterologous antibodies in these specimens of serum are in any different proportion from that which would be found in a comparable group of normal specimens. Antibody for herpes simplex and diphtheria antitoxin are both much more frequently found in children from crowded industrial suburbs than in those from better class areas. In the industrial areas herpes infection is contracted before the age of 2 years, while diphtheria antitoxin appears as a rule only after the child has begun to attend school. There is no association between the frequency of antibody for swine influenza or of staphylococcic antitoxin in serum and the nature of the social environment. There is a significant correlation between the presence of antibody for poliomyelitis and that of diphtheria antitoxin in young children from industrial suburbs; this suggests that the two antibodies are acquired at about the same age and under similar environmental conditions.

GONCE JR., Madison, Wis.

SOME STATISTICAL FACTS CONCERNING WHOOPING COUGH IN NEW SOUTH WALES. E. S. A. MEYERS, M. J. Australia **2**:468 (Sept. 23) 1939.

The general public still displays an attitude of indifference to whooping cough, which contrasts strangely with the fact that it is undoubtedly one of the most distressing and fatal of the acute infections of childhood. In the period from 1889 to 1938 there were 27,108 deaths in New South Wales from the four common infectious diseases of childhood (diphtheria, scarlet fever, whooping cough and measles), of which 20,940 (77.3 per cent) occurred among children under the age of 5 years. Of the total number of deaths, whooping cough was responsible for 8,727, a number which is exceeded only by the number of deaths due to diphtheria (11,849). In the "under 5 years" group whooping cough was the cause of 8,438 deaths, which exceeds the 8,025 deaths due to diphtheria in the same age group. For the period from 1928 to 1937, whooping cough killed 1,189 children aged under 3 years, as compared with 754 whose deaths were due to diphtheria. During this same period 61.7 per cent of all deaths due to whooping cough occurred during the first year of life.

GONCE JR., Madison, Wis.

STEATORRHEA. F. S. HANSMAN, M. J. Australia **2**:677 (Nov. 4) 1939.

Hansman presents a fine discussion of the current ideas on the physiologic phenomena concerned with the ingestion, digestion, absorption and excretion (including methods of determination) of fats.

GONCE JR., Madison, Wis.

PATHOLOGIC LESIONS OF MUMPS. V. DE LAVERGNE, P. KISSEL and P. LEICHTMAN. Presse méd. **47**:961 (June 17) 1939.

The parotid gland of a 7 year old girl with mumps was examined. The most apparent lesions were in the interstitial connective tissue and consisted of edema, capillary dilatation and an infiltration of lymphocytes and plasma cells. Where this infiltration pressed too closely on the acini, necrosis occurred. Because of the similarity of the lesions to those observed in the salivary glands in the course of rabies and the absence of primary lesions in the small ducts, the authors advance the thesis that mumps is caused by a virus which travels along the nerve paths.

DAFFINEE, Boston.

THE PUBLIC AND IMMUNIZATIONS. A. TOURAINE, Presse méd. **47**:1117 (July 15) 1939.

In France arguments are rife as to the merits or dangers of the compulsory administration of diphtheria toxoid, as provided for under the law of June 1, 1938. Touraine presents figures to show how previous laws providing for compulsory immunizations have been obeyed. In his investigation 572 patients were questioned.

Vaccination against smallpox was made compulsory by the law of Feb. 15, 1902. The whole French population and foreigners residing in France are required by the law to be vaccinated in the first, the eleventh and the twenty-first years of life. Of 305 men, 1 (a foreigner) had never been vaccinated; 15 others (13 foreigners) had been vaccinated only once; 64 had been revaccinated once, and 169 twice; 51 had been revaccinated three times or more. Of 267 women, all had been vaccinated once, but 4 (all foreigners) had never been revaccinated once, and only 68 twice.

Typhoid vaccination is compulsory only for those in military service but is easily available to the civilian population. On this point 404 men were questioned; 245 had been immunized once, and 7 had been given a second course of vaccine. Of 346 women included in the study, only 13 had been immunized.

DAFFINEE, Boston.

MEDICAL THERAPY IN INFANTILE PARALYSIS. P. TOLENTINO, Lattante **10**:370 (Sept.) 1939.

Medical therapy in infantile paralysis has been directed toward (1) combating the disease in its acute phase, either by attacking the virus or by building up the body defenses, (2) overcoming the anatomic-pathologic lesions by relieving pressure on the nerve cells, (3) stimulating the involved cells and (4) relieving the symptoms of the disease, as excitability, pain, poor circulations and respiratory difficulty. American workers have quite satisfactorily shown that serum therapy is of little or no value in the treatment of infantile paralysis. However, Tolentino recommends that the use of serum be not wholly abandoned and suggests that various new methods of chemotherapy be tried in the hope that benefit may ensue.

HIGGINS, Boston.

BACTERIOLOGIC DIAGNOSIS OF MALIGNANT DIPHTHERITIC ANGINA. M. A. JAUREGUY and R. ETCHELAR, Arch. de pediat. d. Uruguay **10**:109 (Feb.) 1939.

Diphtheria in Uruguay has increased in frequency and severity during the past decade. Very severe and malignant types of diphtheria are not uncommon. From a practical standpoint the early clinical diagnosis is important and often more valuable than the bacteriologic. The latter is often negative in the early stage. The outcome of the malignant form depends much on early specific treatment. The authors regard clinical diagnosis as far more dependable than laboratory diagnosis, especially in the early stages of grave, malignant diphtheritic angina.

SCHLUTZ, Chicago.

PRACTICAL RESULTS OF DIPHTHERIA VACCINATION. J. J. LEUNDA and O. V. RAGGIO, Arch. de pediat. d. Uruguay **10**:277 (May) 1939.

Diphtheria exists in the population of Uruguay both in grave and in epidemic form. The most efficient method of defense against it is immunization. Immunization in the infant is harmless and effective. It can be undertaken as early as the ninth month. The authors advise the use of antitoxin in three doses of 1, 1.5 and 2 cc. at twenty day intervals. This type of immunization offers practically certain immunity. In older children, beyond 10 years, and in adults, who often show an unfavorable reaction to immunization, it is wise to begin with smaller doses and carry the immunization over a longer period.

The use of two doses of the antitoxin or of the toxoid, or of both of these in combination, assures a certain degree of immunity against diphtheria. If for various reasons only one dose can be given, the authors recommend the use of alum-precipitated toxoid. With this preparation immunity is not altogether certain. The effectiveness of the immunization is controlled by the reaction to the Schick test.

SCHLUTZ, Chicago.

A REMARKABLE PAPULAR BLANCHING PHENOMENON IN SCARLET FEVER. L. M. KUGELMEIER, München. med. Wchnschr. **86**:1575 (Nov. 3) 1939.

Horse serum scarlet fever antitoxin, 0.5 cc., was injected into the skin of a patient with a scarlet fever rash on the third day of the disease. On the following day the site of injection was surrounded by an intense redness of 4 cm. in diameter. During the next two days there developed at the point of injection a lentil-sized red papule and surrounding this an area of blanching about the size of a mark piece. This in turn was surrounded by a red zone 2 cm. in diameter. This remarkable phenomenon persisted for two days after the rash disappeared. According to the author, such a reaction has never been obtained with serum but was described after the intracutaneous injection of calcium gluconate.

BRAHDY, Mount Vernon, N. Y.

## Acute Infectious Diseases

BACILLARY DYSENTERY DEVELOPING IN MONKEYS ON A "VITAMIN M" DEFICIENT DIET. M. JANOTA and G. M. DACK, J. Infect. Dis. **65**:219 (Sept.-Oct.) 1939.

Captive monkeys of the species Macaca mulatta may be carriers of Bacterium dysenteriae (Flexner). Carriers on a "vitamin M"–deficient diet generally presented bacillary dysentery caused by Bact. dysenteriae (Flexner) X type. Some animals are more readily depleted of vitamins than are others. Monkeys on diets deficient in "vitamin M" and one or more of vitamins A, C and D did not react differently as far as lesions of the colon and infection with Bact. dysenteriae were concerned than did monkeys on only the "vitamin M"–deficient diet.

TOOMEY, Cleveland.

PSITTACOSIS IN IMPORTATIONS OF PSITTACINE BIRDS FROM THE SOUTH AMERICAN AND AUSTRALIAN CONTINENTS. K. F. MEYER and B. EDDIE, J. Infect. Dis. **65**:234 (Nov.-Dec.) 1939.

A consignment of 62 psittacine birds from Queensland, Australia, lost 7 birds en route and 24 within twenty-five days after landing. Since the major cause of the mortality was attributable to psittacosis, there was every warrant for destroying the entire shipment. With better knowledge, it may be practical in the future to cull the infected parrots from such a shipment with the aid of the complement fixation test.

TOOMEY, Cleveland.

GIARDIASIS IN CHILDREN. R. CHATTERJI, Indian J. Pediat. **6**:158 (July) 1939.

In a series of 200 consecutive patients admitted to the Children's Hospital, Calcutta, 10.5 per cent showed Giardia infestation. The highest incidence was at 4 to 5 years and the next highest at 1 to 3 years. The symptoms included acute and chronic gastroenteritis, hypochromic anemia, malnutrition, edema of the feet and pain in the abdomen and joints. The stools varied in number from two to fifteen daily; they were pale, offensive and fairly large. Two closely resembled those associated with sprue. The blood picture did not show eosinophilia. Acetarsone given twice daily for a week cured a majority of the patients. Atabrine was tried in several cases with great success and will be the subject of a forthcoming report.

GONCE, Madison, Wis.

CHEMOTHERAPY IN PLAGUE INFECTION. HARRY SCHUTZE, Lancet **1**:126 (Feb. 4) 1939.

It was found that sulfapyridine produced results comparable with those of antiplague serum against infection with Bacillus pestis in rats and mice. The drug was given both with the food or drink and by subcutaneous injection.

LANGMANN, New York.

MALARIAL NEPHRITIS (NEPHROSIS) IN THE SOLOMON ISLANDS AND MANDATED TERRITORY OF NEW GUINEA. C. S. JAMES, M. J. Australia **1**:759 (May 20) 1939.

James reviews 22 cases of malarial nephritis observed among natives of islands of the southwestern Pacific. The chief findings were edema, ascites, albuminuria, enlarged spleen, anemia, normal values for blood nitrogen and normal blood pressure. The blood films showed malarial parasites (usually of the quartan variety) in 53 per cent of cases. Eighty per cent of the patients were children under 7 years of age. The history of the signs of nephritis was short, but that of the signs of malaria was long. When quinine was given by mouth in 8 cases, 5 patients died. When quinine was given by intramuscular injection in 14 cases, 1 patient died. Efficient quinine therapy plus atabrine, when necessary, brought about dramatic recovery. The author believes that much nephritis in the southwestern Pacific is due to malaria and should be treated by daily intramuscular injections of quinine until the edema has subsided and until the quinine can be absorbed when given by mouth.

GONCE, Madison, Wis.

UNDULANT FEVER IN CUBA. T. VALLEDOR and M. CHEDIAK, Arch. de med. inf. **88**:193 (Sept.) 1939.

This study was initiated because a 6 year old boy contracted undulant fever, the first child with the condition to be reported in Cuba. The diagnosis of the disease was confirmed by agglutination tests. The treatment consisted of injections of sodium cacodylate U. S. P. (0.20 Gm. every other day).

Although the disease occurs frequently in cattle in Cuba, only 13 cases have been reported in human beings. This low incidence is due to the custom in Cuban families of boiling their milk, although sometimes the condition may have been mistaken for a form of typhoid fever.

SANFORD, Chicago.

TWO CASES OF MALARIA IN EARLY CHILDHOOD. I. TOMA, N. NICOLAE and F. MEDESAN, Med. inf., Bucuresti **1**:310 (July-Aug.) 1939.

The malarial infection was confirmed by laboratory examination. The disease was characterized by attacks of atypical fever in one child, an infant of 6 months, accompanied only by depression and anemia, and by typical fever in the other, a child of 18 months. Regarding the source of infection, it is probable that the children were infected while at an institution, for the ages indicate that it is a

little late to consider placental transmission of the infection. Transmission by hemotherapy is improbable in view of the history of the donors. The institution is situated only 500 meters from poorly drained marshes, and the children were frequently out in the garden, so that mosquitoes are the most probable source of the infecting parasites.

Quinine treatment had little effect, but when the method of d'Ascoli was used, the children promptly recovered.

LESLIE, Evanston, Ill.

SEASONAL INCIDENCE OF KALA-AZAR IN INFANTS AND ITS SIGNIFICANCE IN RELATION TO THE TRANSMISSION PROBLEM OF THE DISEASE. I. C. YUAN, F. T. CHU and C. U. LEE, Chinese M. J. **56**:241 (Sept.) 1939.

This study of kala-azar occurring in the first year of life comes from the department of public health and medicine of Peiping Union Medical College. The writers call attention to the simplicity of the eticlogic factors, such as the diet and environment of the infant, which makes the epidemiology of kala-azar not complicated. The personal history given by the mother of an infant is short and recent, and the duration of the disease has been so brief that seasonal or other factors during the year may be ascertained.

The authors analyzed 36 cases of kala-azar in infants encountered in the period from 1923 to 1938 in which Leishmania donovani was isolated. Other criteria required that no more than six months should have elapsed between the onset of symptoms and the first medical examination; the date of birth was known, and the fact of the onset during the first year of life.

The authors find that there is a period of greatest infectivity for infants during the early summer and that in June and July a species of sandfly, Phlebotomus chimensis, is naturally infected with L. donovani in houses in which kala-azar is found. It is thought that these facts are significant for man in North China, facts which are advanced for the first time from a study of cases of this disease in man.

Hospital reports of the 36 cases are given in the 9 concluding pages of the authors' paper.

NEFF, Kansas City, Mo.

THE ANEMIA OF ACUTE RHEUMATIC FEVER IN CHILDREN. G. GEZELIUS, Acta pædiat. **23**:361, 1939.

Virtually all of the infectional diseases of childhood produce an acceleration of the sedimentation rate of the erythrocytes. Also, most infections occurring during the same period of life result in a greater or lesser degree of anemia. However, acute rheumatic fever is notorious for the rapidity with which anemia appears after the onset of illness and the profound reduction of hemoglobin that may take place within a comparatively short time. In a group of 31 children suffering from acute rheumatic fever, Gezelius observed the rapid development of anemia in 22. Nonmathematical comparison of the results of serial blood counts and measurements of the sedimentation rate revealed a high degree of inverse correlation between the concentration of hemoglobin and the sedimentation rate in these patients. With subsidence of the infection, as the sedimentation rate returned to normal the hemoglobin climbed spontaneously to levels characteristic of health. Blood regeneration was not influenced by the administration of reduced iron during the acute stage of the disease. The author feels that measurements of hemoglobin can be used as a check of the significance of increased sedimentation rates; the latter are somewhat too sensitive and may be influenced by intercurrent infections not directly related to acute rheumatic fever.

MCCUNE, New York.

A NOSOCOMIAL EPIDEMIC OF PARATYPHOID. N. FAXÉN, Nord. med. tidskr. **16**:1092 (July 9) 1938.

Faxén reports an epidemic of paratyphoid at a maternity hospital originating from a bacilli-carrying puerperant. The epidemic involved 23 adults and 15 new-

born infants. The contagion was probably transmitted during the mother's stay at the hospital and evidently by contact, although some of the infants may have been infected by breast milk. The mothers of 7 of the infected infants were themselves free from infection. In all the infants but 1 the infection did not produce morbid symptoms although bacilli were excreted for some time, in 1 case for seven months. The infant who fell ill (breast fed only for a short period) died from paratyphoid meningitis. Paratyphoid fever in a lactating mother does not necessitate weaning the baby, as the latter often is infected at the time the disease is diagnosed in the mother and the symptoms of the infection in young infants are slight.

WALLGREN, Göteborg, Sweden.

## Chronic Infectious Diseases

SYPHILIS OF THE SKELETON IN EARLY INFANCY: THE NONSPECIFICITY OF MANY OF THE ROENTGENOGRAPHIC CHANGES. J. CAFFEY, Am. J. Roentgenol. **42**:637 (Nov.) 1939.

Roentgenograms of 550 nonsyphilitic infants were studied. These infants were syphilis free as determined by clinical and serologic examinations of the infants and their families (when available). These roentgenograms show changes indistinguishable from syphilitic osteochondritis, syphilitic osteomyelitis and syphilitic osteoperiostitis.

Syphilitic osteochondritis in its most frequent forms was simulated by staphylococcic bacteremia, pneumococcic bacteremia, hematogenous tuberculosis, erythroblastosis foetalis, septic hemolytic anemia, familial hemolytic anemia, multiple birth injuries, congenital atresia of the biliary tracts, severe malnutrition, unexplained hemiparesis and protozoan encephalitis, as well as in the newborn delivered of a mother who had bismuth therapy during gestation. In this nonsyphilitic group no conditions were found simulating syphilitic osteochondritis of the type which is expressed in (1) "saw tooth" metaphyses, (2) foci of rarefaction in angles of the cartilage-shaft junction and (3) multiple infractions through the ends of the shafts.

Diffuse syphilitic osteoperiostitis was simulated by healing rickets, prematurity, an undiagnosed disorder of nutrition, traumatic periostitis of the newborn and erythoblastic anemia.

Osteoperiostitis callosa was simulated by multiple osteomyelitis due to the gonococcus.

Syphilitic osteomyelitis was simulated by multiple pyogenic osteomyelitis. Pomeranz expressed the opinion that syphilis and tuberculosis of the metacarpals, metatarsals and phalanges cannot be differentiated roentgenographically.

Roentgen evidence of syphilitic involvement of the skeleton is not conclusively diagnostic of infantile syphilis and should not be the sole criterion for the administration of antisyphilitic therapy.

When osteochondritis, osteomyelitis and osteoperiostitis are present in combination, they are more indicative of syphilis than only one of these lesions would be.

SQUIRE, Chicago.

COMMON FORMS OF CHILDHOOD TUBERCULOSIS. B. SCHICK, M. Clin. North America **23**:645 (May) 1939.

The ideal procedure for the detection of early tuberculous infection is the regular testing of all children under his care by the family physician. This testing should be obligatory for children who stop gaining in weight and suffer from lassitude, accompanied by a diminishing of turgor of the tissues, without obvious cause. The safest way to discover tuberculosis in a child is to perform a Pirquet test with concentrated old tuberculin. Should this test prove negative, a Mantoux

test should be made within twenty-four to forty-eight hours after the Pirquet test. If more time has elapsed, the Pirquet test should be repeated, since the small amount of tuberculin absorbed increases the cutaneous sensitivity to tuberculin. Schick's experience with the "patch test," as developed by Vollmer, has been so satisfactory that he believes that it will become the "test of choice" for the practitioner.

Certain clinical manifestations in children should suggest the presence of tuberculous infection. In infants and in children in the second year of life, papulonecrotic tuberculids may be found, particularly on the extremities and about the anal region. These lesions are small, resembling brownish red pimples, and show a necrotic center. They are the result of a lymphogenous or hematogenous invasion of the tubercle bacilli and are therefore of serious import. In older children other varieties of tuberculous cutaneous lesions may appear. Lesions in the eye, such as phlyctenula, should not be overlooked. Erythema nodosum should be considered a tuberculous manifestation unless it can be proved not to be.

An important diagnostic symptom is "expiratory dyspnea" accompanied by a high pitched brassy cough, suggesting whooping cough, but without whoop or vomiting. This symptom is due to the presence of enlarged lymph nodes, located usually at the bifurcation of the bronchi.

Chronic enlargement of the cervical lymph nodes should be investigated and its nature determined. If it is due to tuberculous infection, the mediastinal and mesenteric nodes may be similarly infected.

The presence of a serous exudate within the pleural or abdominal cavities is an indication for careful tuberculin testing. Swelling of the testicles is not a rare manifestation of tuberculous disease.

The author states that with proper equipment for the diagnosis of tuberculosis in childhood at hand there should be no difficulty in discovering whether any given disease is of a tuberculous nature. The detection of tuberculosis in children frequently gives a clue to its existence in the family or in the environment, thereby proving its value as a public health measure.

EUGENE H. SMITH, Ogden, Utah.

TUBERCULIN TESTING IN PUBLIC SCHOOLS. J. L. WILSON, New Orleans M. & S. J. **92**:244 (Nov.) 1939.

In a symposium on tuberculosis Wilson reports his experience with tuberculin testing in the public schools of New Orleans.

Although the campaign disclosed few cases of active tuberculosis he feels that such a procedure is of great value for two reasons: 1. It finds the children with tuberculosis early and affords the opportunity of isolating them from other children. 2. It educates the parents and children to the importance of detecting tuberculosis in the community.

In this year's tests of 2,128 students, 35 per cent of the white and 50 per cent of the colored students reacted positively.

BERKLEY, Los Angeles.

POTT'S DISEASE IN CHILDREN. G. K. SMITH, M. J. Australia **2**:303 (Aug. 26) 1939.

Pott's disease is essentially a disease of childhood, although frequently it is prolonged into adult life. In regard to symptoms, it is important to note their scarcity until the destruction of the vertebral bodies is well under way. Deformity was present in 80 per cent of the patients on admission to the hospital. Complications seen were largely those of abscess formation. The author is distinctly discouraged over operative treatment, but is emphatically in favor of fixation apparatus until healing is complete.

TENNEY, Madison, Wis.

THE IDE REACTION IN CONGENITAL SYPHILIS. G. ERNANDEZ and D. JONAS, Monatschr. f. Kinderh. **79**:196 (Aug.) 1939.

Comparing the Ide with the Wassermann and the Meinicke reactions, the writers found a 94 per cent agreement in sensitivity and a 91 per cent agreement in specificity. Inasmuch as the technic of the Ide reaction is quite simple, the writers recommend it.

GERSTLEY, Chicago.

TUBERCULOSIS OF FIRST INFECTION AND OF REINFECTION; THEIR FREQUENCY IN CHINESE PEOPLE OF PEKING. E. L. OPIE, Chinese M. J. **56**:197 (Sept.) 1939.

Opie, of Cornell University, the visiting professor of pathology at Peiping Union Medical College, has two articles in this number of the *Chinese Medical Journal,* the first dealing with tuberculosis of the city population and the second with adults only of the Chinese rural population. In the first paper he reports on the lesions in the Chinese of Peiping as regards frequency of the childhood type (first infection) and the adult type (reinfection), both at different periods of life.

Opie had found in the United States that mortality in childhood reaches its peak in the second six months of life, dropping thereafter suddenly to reach a lower incidence in the years from 5 to 12 than at any other period of life.

If a person escapes tuberculosis in childhood and is attacked later in life, he may show the type of tuberculosis that is characteristic of infancy. The author reproduces four drawings, made at autopsy, of adults whose lungs showed the first infection type.

Tables are given of the types of lesions found in males and females at 1,000 autopsies for 1935 to 1939, including children and adults.

NEFF, Kansas City, Mo.

PULMONARY TUBERCULOSIS IN CHILDREN WITH A SPECIAL VIEW TO THE PROGNOSIS. S. HOLM, Acta pædiat. **23**:455, 1939.

This survey comprises 267 children admitted to the Fuglebakken Hospital between 1928 and 1936. All of them had positive tuberculin reactions, and all showed roentgen features compatible with mediastinal or pulmonary tuberculous infection. In 233 cases tubercle bacilli were demonstrated in the gastric contents, either culturally or by animal inoculation; in 22 additional cases the organism was visible on direct microscopic examination of material obtained by lavage of the stomach.

All survivors were reexamined in the autumn of 1937. At the time of reexamination, 51 of the 267 children had died, 46 of tuberculous meningitis or miliary tuberculosis and 5 of pulmonary disease. Of the children whose disease had been fatal 40 died within six months after admission and 48 within one year. The prognosis was found to differ greatly according to the age on admission to the hospital; of 55 infants under 1 year, 24 died, and of 30 children aged 7 to 14 years, only 1 died. By way of contrast, the 216 survivors included only 9 who were still infected. These results suggest the conclusion that if children survive the first year of their infection the remote prognosis is good.

With regard to the prognostic importance of given symptoms that may become manifest during the critical first year of illness, the following conclusions appear justified: roentgen evidence of extension of the tuberculous process is of decisive importance, whereas the precise location of the lesion has little effect on the outcome. Miliary dissemination throughout the lungs is not invariably fatal; in this series 2 of 19 patients recovered. Exudative pleurisy is a benign manifestation. The demonstration of tubercle bacilli by direct microscopic examination of the stomach contents possesses grave significance. The sedimentation rate of the erythrocytes has little prognostic value. Physical examination of the chest is an

unreliable source of information; the same is true of subjective manifestations of the disease. Bitonal cough in infants and erythema nodosum in older children are the only physical phenomena that suggest with any degree of clarity the existence of pulmonary tuberculosis.

Apart from meningitis, extrapulmonary complications were uncommon in this series, and they did not appear to aggravate the prognosis. Of 167 cases in which the source of the infection was identified, it was found to have been within the family in 120. With regard to children more than 1 year of age the prognosis did not appear to be more grave on this account. McCUNE, New York.

## Diseases of Blood, Heart and Blood Vessels and Spleen

INCIDENCE OF ORGANIC HEART DISEASE IN SCHOOL CHILDREN. L. W. RAUH, Am. Heart J. **18**:705 (Dec.) 1939.

Of a total of 85,389 school children living in Cincinnati, 449 were found to have organic heart disease. Acquired heart disease, probably rheumatic in origin, was found in 55 per cent; congenital heart disease, in 45 per cent.

Acquired heart disease was more prevalent in the Negroes than in the white children, was more frequent in girls than in boys and was found more often among the poor than among the well-to-do.

The incidence of congenital heart disease was independent of race or sex.

A comparison of the results of this study with those of previous school surveys indicates that there are wide variations of incidence in different localities.

GIBSON, Chicago.

THE VALUE OF THE WELTMANN SERUM COAGULATION REACTION AS A LABORATORY DIAGNOSTIC AID; COMPARISON WITH THE SEDIMENTATION RATE. S. A. LEVINSON and R. I. KLEIN, Ann. Int. Med. **12**:1948 (June) 1939.

Weltmann states that by means of the Weltmann serum coagulation test a distinction can be made between exudative processes, on the one hand, and fibrotic processes or parenchymatous liver damage, on the other. In addition, the test is roughly quantitative, and reflects the degree of exudation present. The technic of the test is given.

The normal coagulation band is between tubes 6 and 6½. In cases of acute inflammatory and exudative conditions there is a shift to the left, or a shortened coagulation band; in cases of chronic diseases distinguished by fibrotic processes and in cases of acute infections in a healing stage, of sepsis and of parenchymatous liver damage, there is a lengthening of the coagulation band, or a shift to the right.

The test is more accurate than the sedimentation test in reflecting pathologic-anatomic changes. READING, Galveston, Texas.

APLASTIC ANEMIA TREATED WITH DAILY TRANSFUSIONS AND INTRAVENOUS MARROW; CASE REPORT. E. C. OSGOOD, M. C. RIDDLE and T. J. MATHEWS, Ann. Int. Med. **13**:357 (Aug.) 1939.

A white girl aged 19 years received forty-three blood transfusions, totaling almost 22 liters of blood, in fifty-two days. In addition, 18 cc. of sternal marrow was given intravenously on one occasion, with no untoward reaction. Polycythemia and enlargement of the spleen developed during the course of the treatment. Despite the large amount of blood transfused, the leukocyte and platelet counts remained at a constant low level. Death resulted from intercurrent infection.

READING, Galveston, Texas.

SCHÜLLER-CHRISTIAN'S DISEASE: REPORT OF A CASE IN ONE OF IDENTICAL TWINS. A. B. JONES, Ann. Int. Med. **13**:1068 (Dec.) 1939.

The twin with Hand-Schüller-Christian disease was aged 20 months. Two siblings, in addition to the other twin, were normal. Roentgenograms of the skull and long bones along with laboratory data are included in the article.

READING, Galveston, Texas.

HISTOPLASMOSIS OF DARLING. F. J. SHAFFER, J. F. SHAUL and R. H. MITCHELL, J. A. M. A. **113**:484 (Aug. 5) 1939.

The fourth case of histoplasmosis of Darling to be reported in the United States and the eighth in the literature is presented, with a discussion of the literature, the clinical and laboratory findings and the resemblance to kala-azar.

HEERSMA, Kalamazoo, Mich.

COOLEY'S ANEMIA (MEDITERRANEAN ANEMIA), WITH A REPORT OF A CASE IN AN ADOLESCENT. E. J. TALHEIMER, A. MEZZETTI and J. GERSHON-COHEN, J. Pediat. **14**:349 (March) 1939.

A case is reported of Cooley's anemia in a girl 14 years of age. She presented all the striking characteristics of the disease. The literature of erythroblastic anemia is reviewed and mention made of 6 other cases of this disease occurring in patients over 14 years of age.

RAUH, Cincinnati.

EFFECT OF CARBON TETRACHLORIDE ON THE SERUM AMYLASE OF DOGS. J. O. HANSON, Proc. Soc. Exper. Biol. & Med. **42**:21 (Oct.) 139.

Carbon tetrachloride administered to dogs was found to cause a decrease in the amylase of the serum; this occurred whether it was given by mouth or subcutaneously. There was no effect on the blood sugar, but the author suggests that the action on the serum amylase may be due to injury of the liver.

HANSEN, Minneapolis.

CIRCULATION TIME UNDER CONDITIONS OF WORK AND REST IN SUBJECTS WITH NORMAL AND ABNORMAL HEARTS. E. F. CANNON, S. P. LUCIA and E. H. BENSON, Proc. Soc. Exper. Biol. & Med. **42**:237 (Oct.) 1939.

The circulation time was determined by intravenous injections of calcium gluconate in 20 normal subjects and in 48 patients with various types of heart disease when at rest and after a definite type of exercise, then again after a five minute rest period. It was concluded that the difference induced in the circulation time after exercise was slight and was not significant as a test of cardiac efficiency.

HANSEN, Minneapolis.

MALIGNANT ENDOCARDITIS WITH CONGENITAL CARDIOPATHY. H. GRENET, R. LEVENT, F. JOLY and COMBES HAMELLE, Arch. de méd. d. enf. **42**:449 (July) 1939.

The authors report a case of this condition in a young girl who had been under observation for almost five years on account of a congenital cardiac lesion. The latter anomaly was consistently diagnosed throughout this period as patent ductus arteriosus. At the age of 17½ years the patient entered the hospital with evidences of an acute infection: there were prostration, high temperature and enlargement of the liver and spleen. Culture of the blood revealed the presence of a nonhemolytic streptococcus. After eleven days purpuric spots appeared, pneumonia developed and the girl died. Autopsy confirmed the diagnosis of patent ductus.

AMESSE, Denver.

PSEUDOLEUKEMIC ANAEMIA. I. GRACOSKI, M. and M. CAMNER, Bull. Soc. de pédiat. de Iasi **9**:18, 1938.

An infant of 7 months had fever, malnutrition, severe rickets, numerous fractures, anemia, a hemoglobin content of 45 per cent, a large spleen, numerous myelocytes and nucleated red cells. Death occurred while the child was under observation, but no autopsy was permitted. LESLIE, Evanston, Ill.

PRINCIPLE OF CASTLE PROVED BY TECHNIC OF SINGER TO BE PRESENT IN THE GASTRIC JUICE OF INFANTS WITH ERYTHROBLASTIC ANEMIA. R. SCAPATICCI, Lattante **10**:349 (Aug.) 1939.

Free hydrochloric acid was absent in the gastric juice of 3 infants 1 year of age with Cooley's anemia. When the filtered gastric juice was injected into rats, the blood of these animals showed a prompt and marked reticulocytic reaction. HIGGINS, Boston.

LIPEMIA IN CHILDREN UNDER PHYSIOLOGIC CONDITIONS. O. MALAGUZZI-VALERI, Riv. di clin. pediat. **37**:833 (Oct.) 1939.

Extensive tables are given, recording data available in the literature on the fats of the blood of children between birth and the age of 7 years. Malaguzzi-Valeri adds 78 observations of his own. Fatty acids and neutral fats of the blood tend to diminish from a mean value of 268 to 188 mg. per hundred cubic centimeters between birth and the age of 10 years. The total cholesterol and phosphatides tend to increase from 86 to 108 mg. and from 172 to 214 mg. per hundred cubic centimeters, respectively, during the same time. The free cholesterol remains practically constant. HIGGINS, Boston.

ACTUAL STATE OF ANGIOCARDIOGRAPHY. AGUSTIN CASTELLANOS and RAUL PEREIRAS, Arch. de med. inf. **8**:250 (Sept.) 1939.

The authors review the work that has been previously published by them in this journal. They conclude that angiocardiography offers the best method for diagnosing congenital heart disease in infancy. The younger the child the better the details; after the age of 8 years the contrasts are poorer. The technic is not difficult, and there is no danger. The method has passed the experimental stage and can be employed by hospital or laboratories. SANFORD, Chicago.

CONGENITAL CARDIAC BLOCK. MAURICIO MANGUEL, Rev. méd. latino-am. **24**:1018 (July) 1939.

In a case of heart block diagnosed by modern methods one should determine whether the condition is congenital or acquired. Of congenital origin, it appears at an early age and is associated with a slow pulse and crises of syncope; there is absence of any disease capable of affecting the heart muscle, conduction system or coronary circulation (rheumatic fever; diphtheria; hereditary syphilis). The most common cause of auricular-ventricular block or disturbance in the bundle of His is Roger's disease, interventricular communication. DWYER, Kansas City, Mo.

CONGENITAL HEART DISEASE ASSOCIATED WITH SUDDEN DEATH. S. LYSS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **31**:248, 1939.

The cases discussed in this article were encountered in 20,000 postmortem examinations made at the Hafenkrankenhaus, Hamburg, Germany, from 1901 to 1938. The anomalies were grouped as (*a*) defects responsible for death, (*b*) defects incidental to death and (*c*) patent foramen ovale. The last group was studied intensively only for the years 1936 and 1937. There were 11 cases in the first group, and in most of them septal defects and various distortions of the chambers

of the heart were presented. When they occurred in children, they were noted during the first few hours or days of life, although their occurrence in stillborn infants was also observed. The only adult showing such an anomaly was a man 21 years old, who had pulmonary stenosis.

The second group included 22 persons with incidental cardiac and vascular defects which fell into the following categories: (*a*) ventricular septal defects, (*b*) atresia of the aortic isthmus, (*c*) aortic stenosis, (*d*) anomalies of valves and (*e*) patent ductus Botalli. This group contained a preponderance of adults except in the last division, in which there were 4 adults and 4 children.

Patent foramen ovale was found 78 times in 2,015 autopsies, an incidence of only 3.5 per cent. In 2 of the cases it was associated with paradoxic embolus. The low percentage is at variance with the observations of Aschoff, who placed the incidence between 20 and 30 per cent.

GEORGE J. RUKSTINAT. [ARCH. PATH.]

THE SUPRAVITAL TECHNIC AND ITS APPLICATION IN HEMATOLOGIC DIAGNOSIS. S. I. DE VRIES, Nederl. tijdschr. v. geneesk. **83**:3207 (June 24) 1939.

This is a description of the supravital method and of the cells in the normal and in the pathologic blood picture. The clinical and hematologic application of the method is emphasized. The special importance of the method is that it makes possible a differentiation of the mononuclear cells. The supravital technic may therefore be of great aid in the study of acute leukemias, chronic leukemic reticuloendotheliosis, infectious mononucleosis and other conditions in which atypical mononuclear cells appear in the peripheral blood. No use is seen for the supravital technic as a routine laboratory method.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Nose, Throat and Ear

ALLERGY OF THE UPPER RESPIRATORY TRACT IN INFANCY AND CHILDHOOD. G. PINESS and H. MILLER, J. A. M. A. **113**:734 (Aug. 26) 1939.

Comparing the incidence of attempts at surgical cure of allergic conditions at the present time with that in the past, the authors deplore the fact that 43 per cent of asthmatic patients were advised to have tonsillectomies to relieve their asthma. They and others find the promises of relief unfulfilled.

Part of the difficulty is caused by confusing the symptoms of allergy with those of infection and those of the combination of the two conditions. The authors urge physicians to recognize the signs of allergy and not to be swept away into a preference for tonsillectomy, blinded to the actual cause of disease of the upper respiratory tract.

HEERSMA, Kalamazoo, Mich.

ROLE OF HEREDITY IN STUTTERING. S. E. NELSON, J. Pediat. **14**:642 (May) 1939.

Two hundred and four stuttering persons were matched in age and sex with nonstutterers. Those belonging to the first group were selected because they stuttered; those belonging to the second were selected because they spoke normally and had no history of stuttering. In the stuttering group there were 163 males and 41 females, ranging from 4 to 30 years of age. Information was obtained in the home of each person, and added information was secured from grandparents, uncles, aunts and friends. The data obtained from comparisons of stutterers whose ancestry showed stuttering with those stutterers whose ancestry was free from this speech defect indicated that there must be some biologic tendency to stutter. Nelson draws the following conclusions from this study:

"1. A greater percentage of stutterers from families showing stuttering in their ancestry began to stutter when learning to speak than those stutterers whose families showed no stuttering in their ancestry.

"2. A greater percentage of stutterers with negative family history began to stutter after the onset of speech than those with a positive family history.

"3. In the group of stutterers with negative family history a greater number began to stutter after the onset of speech than at the time of onset of speech.

"4. There is a constant ratio in favor of the greater incidence of disease and other precipitating factors occurring at the incidence of stuttering in stutterers with negative family history than in those with stuttering in their ancestry.

"5. A significant percentage of stutterers with negative family history showed a history of diseases and other precipitating factors which occurred with the incidence of stuttering after the onset of speech as compared with the percentage of stutterers belonging to the group with stuttering in the ancestry.

"6. A significant percentage of stutterers with positive family history showed a history of no diseases or precipitating factors coincident with the onset of speech and stuttering as compared with the group whose family history is negative.

"7. The accidents, frights and diseases, coincident with the result of stuttering were found to be more violent and severe among the group having a negative family history than among those with a positive family history."

RAUH, Cincinnati.

THE MODE OF ACTION OF X-RAYS IN OTITIS MEDIA. L. L. TITCHE, New Orleans M. & S. J. **92**:203 (Oct.) 1939.

Titche reviews the literature pertaining to the action of roentgen rays on acute infections. Most especially, attention is drawn to the action on infections of the ear. The main action of roentgen rays seems to be to promote liquefaction and absorption of the inflammatory exudate and death of the organisms by destruction of leukocytes with liberation of lysis and antibodies.

The results in a series of 65 cases of aural infection are given. The series consisted of 35 cases of catarrhal otitis, 23 cases of acute purulent otitis and 7 cases of chronic purulent otitis.

The catarrhal patients were normal three days after a single irradiation with an average of 73.62 roentgens. Patients with acute purulent otitis received an average of 1.32 treatments with an average dose of 71.91 r. The ears were dry in nine days. Patients with chronic prurulent otitis received an average of 1.33 treatments with an average of 75.38 r, and the ears were dry in 12.66 days.

The results, according to the author, speak for themselves. Any one may use roentgen treatment and expect results, but this form of therapy should not be relied on exclusively.

BERKLEY, Los Angeles.

MECHANISM OF ESTROGEN EFFECT ON NASAL MUCOSA IN ATROPHIC RHINITIS; SUCCESSFUL TREATMENT WITH PROSTIGMIN. S. SOSKIN and L. B. BERNHEIMER, Proc. Soc. Exper. Biol. & Med. **42**:223 (Oct.) 1939.

Fourteen patients suffering from advanced atrophic rhinitis with ozena were treated from two to six months by spraying 0.25 cc. of a 1 : 2,000 solution of prostigmine methylsulfate into each nostril four times daily. A nasal irrigation with a mild alkaline fluid was given once or twice daily. All patients definitely improved within two weeks; crust formation decreased as did the nasal discharge, and the ozena was controlled. The results were far superior to those from local treatment with estrogenic substance. Previous studies disclosed that the benefit from estrogenic substance in the nasal mucosa was due to (1) specific proliferative effects and (2) effects secondary to hyperemia. The acetylcholine-liberating property of estrone (theelin) probably accounted for the benefit from intranasal estrone therapy in atrophic rhinitis, which thereby produced hyperemia. The authors then reasoned that acetylcholine effects could be obtained by inhibiting the choline esterase, thus the use of a synthetic physostigmine-like substance in this study.

HANSEN, Minneapolis.

## Diseases of Lungs, Pleura and Mediastinum

AYERZA'S DISEASE. E. E. SMITH, J. Pediat. **14**:602 (May) 1939.

Ayerza's syndrome was observed in a 13 year old girl. She had a history of a chronic pulmonary condition, associated with frequent headaches, a characteristic cough, generalized cyanosis, insidious in onset and progressive, polycythemia, dyspnea and absence of clubbing of fingers and toes, and a roentgenogram which revealed evidence of chronic inflammation of the lungs and prominence of the pulmonary conus. Clinically there was no evidence of syphilis. The child died of an acute infection of the respiratory tract, probably pneumonia. No postmortem examination was made.

Smith briefly reviews the literature. Only 1 other case of Ayerza's disease occurring in a child has been reported; this patient was a married Hindu girl 12 years of age who was suffering from syphilis. Although the literature contains no statement of Ayerza's opinion as to the etiologic agent in this syndrome, the weight of evidence is in favor of syphilis with primary sclerosis of the pulmonary artery as the most common causative agent and chronic primary bronchopulmonary changes of varied cause as a less frequent etiologic factor. The syndrome seems to occur only in cases of long-standing pulmonary inflammation associated with sclerosis of the pulmonary arteries.

RAUH, Cincinnati.

BRONCHOGRAPHY IN CHILDREN. H. E. S. PEARSON and H. L. THORNTON, Brit. J. Radiol. **12**:229 (April) 1939.

A method of introducing iodized poppyseed oil into the bronchi of small children is described. Basal anesthesia with paraldehyde administered rectally is followed by 5 per cent cocaine sprayed into the pharynx and nose. Nitrogen monoxide and oxygen anesthesia is then used, and a large intratracheal tube in which a small indwelling catheter lies is placed in the trachea. The anesthetic is administered through the large tube, and the oil is instilled through the small catheter which enters the large tube through a small side opening near the top of the tube. With the child under nitrogen monoxide anesthesia the oil is then injected into the trachea, and its flow is watched and directed by fluoroscopic observation. Any part of the lung can be examined by inverting or turning the child. Films are taken as desired.

SQUIRE, Chicago.

SERUM TREATMENT OF PNEUMOCOCCIC PNEUMONIA IN CHILDREN. J. CLAUSEN, Ann. pædiat. **153**:57 (May) 1939.

The subjects of the present studies were 104 children with pneumonia admitted to the department of pediatrics of the Sundby Hospital, Copenhagen, in the period from Dec. 1, 1937 to Dec. 1, 1938. The presence of pneumococci was demonstrated in 82 of these children. The principal method of typing the pneumococci was by cultivation of material from the throat and larynx. Comparison (by Vammen and the writer) of laryngeal cultures obtained through the laryngoscope with ordinary throat cultures appeared to show that swabbing through a laryngoscope gives a somewhat more reliable diagnosis of type than does swabbing without a laryngoscope, owing to the frequent occurrence of saprophytic pneumococci in the throat.

Cultures of material from the throat and larynx have been supplemented by blood cultures (repeatedly in some cases). In several cases the blood cultures revealed pneumococcic bacteremia, and in some cases blood culture proved to be the method of examination which gave the correct diagnosis of type while culture of throat and laryngeal material gave uncertain or faulty results.

In some cases in which otitis media was accompanied by a discharge from the ear, cultures of the discharge contributed to the diagnosis of type. The dosage of serum employed is mentioned, with the method of administration.

A preliminary report is given of studies (by Björneboe and the writer) on the absorption of antibodies from antipneumococcus serum injected intravenously, intra-

peritoneally and intramuscularly, showing that when intravenous injection is impracticable a more rapid effect may be expected from intraperitoneal than from intramuscular injection.

The importance of assaying the concentration of antibody in the blood of a child during the first few days after treatment with serum is emphasized and illustrated.

Of the 82 cases of pneumonia in which cultures for pneumococcus were positive, 49 in the age class of 2 to 12 years and 33 in the class under 2 years are recorded schematically.

An attempt is made to elucidate the value of serum therapy by dividing the patients with severe uncomplicated pneumonia into a serum-treated group and a control group, through an alternation that made the two groups directly comparable. The comparative studies showed that in the children over 2 years of age the duration of illness was shortened by about two days, whereas the mortality was not found to be influenced by the serum treatment. The infants presented no definite effect from the serum treatment—possibly because the material is so small. Several cases show that serum treatment late in the course of pneumonia offers no decisive protection against subsequent development of empyema.

On the basis of his own findings and the studies reported by other investigators in this field Clausen summarizes the appraisal of the serum treatment and of its significance in childhood as follows: In the treatment of children with pneumonia the antipneumococcus serum does not play the conspicuous role that it does in the treatment of adults, chiefly because of (1) the relatively low mortality from lobar pneumonia in children, (2) the far greater uncertainty of the diagnosis type of pneumonia in children and (3) the comparatively great frequency of mixed infections in infants with pneumonia. Notwithstanding these circumstances and in spite of the risk that will always be associated with the intravenous injection of a heterologous serum, antipneumococcus serum is of value in the treatment of children with severe attacks of pneumonia—especially when given in the first days of illness and, in particular, in the presence of bacteremia.

FROM AUTHOR'S SUMMARY AND CONCLUSIONS.

STRUCTURE OF THE BRONCHIOLAR WALL RELATIVE TO ITS FUNCTION. S. ENGEL, Ann. pædiat. **153**:263 (Aug.) 1939.

The lumens of the bronchioles, the walls of which are not supported by cartilage, are kept patent by the tone of the smooth muscles surrounding the walls, This is the main function and the importance of the bronchiolar musculature. Overdilation in inspiration and collapse in expiration are likewise prevented. This mechanism is of clinical importance, because in the frequent cases of bronchitis and bronchiolitis in infancy and early childhood occlusion of lumens paves the way for collapse and pneumonia. Therapy must take into consideration much more than it has up to the present the part played by these muscles.

FROM AUTHOR'S CONCLUSIONS.

ORIGIN AND DEVELOPMENT OF INFILTRATIONS IN UNIFOCAL (LOBAR) PNEUMONIA. S. ENGEL, Ann. pædiat. **153**:297 (Sept.) 1939.

The triangular opacity in pneumonia involving the upper lobe of the right lung is explained anatomically as an infiltration which arises from the base of the lobe and is arrested toward the apex by a septum separating the anterior-superior from the posterior-inferior part of the lobe.

Anatomic and roentgenologic investigations give a convincing conception of the origin and spread of pneumonia. It originates in a primary localized infiltration, disconnected from the hilus. This again develops preeminently in the posterior part of the lung, near an extensive pleural plane.

The posterior part of the lung is doubly characterized by the shortness of the supplying bronchi and by its lesser aeration, owing to the small respiratory move-

ments of the ribs in the back. The subpleural layer of the lung tissue, with its own network of lymphatics, paves the way for definite spread of the infiltration.

Conditions for spread are best fulfilled in the base of the upper lobe of the right lung and in the lower lobe of both lungs. These lobes are frequently attacked by pneumonia, whereas the upper lobe of the left lung and the middle lobe of the right lung, which do not present such anatomic conditions, are less prone to primary pneumonia.

The chief observations in this paper are presented in the following scheme:

I. Infiltrations of unifocal (lobar) pneumonia do not arise diffusely but from a localized primary infiltration.

II. The "loci preferentiae" for the origin of the primary infiltration are: 1. The angular base of the upper lobe of the right lung. 2. The apexes of the lower lobes of both lungs.

III. These places are characterized: 1. By their position in the posterior, less aerated part of the lung. 2. By the proximity of the hilus, i. e., by short supplying bronchi. 3. By the proximity of large planes of pleura, i. e., the proximity of large areas of subpleural tissue.

IV. The infiltration enlarges at first by concentric growth and thus eventually reaches the subpleural tissue. The subpleural tissue forms the pathway by which infiltration proceeds toward the final stage (cf. III, 3).

V. The formation of annular opacities in the resolution of pneumonia is the result of early resolution of the central parts which, having formed the primary infiltration, are the oldest. This occurs chiefly in cases with protracted resolution.

FROM AUTHOR'S SUMMARY AND CONCLUSIONS.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

USE OF PECTIN-AGAR MIXTURES IN DIARRHEA. G. W. KUTSCHER JR. and A. BLUMBERG, Am. J. Digest. Dis. **6**:717 (Dec.) 1939.

Thirty-two patients with diarrhea were treated by means of a pectin, agar and dextrimaltose addition to whole milk. Sixteen other patients with diarrhea were treated by means of a pectin, agar and whole milk mixture sweetened with saccharin. The stools became normal within three days. The study is not a statistical but a clinical one. The authors' conclusion is that this is a desirable procedure in the treatment of diarrheas, both infectious and noninfectious.

MORRISON, Savannah, Ga.

FOUR OUTBREAKS OF FOOD POISONING TRACED TO ONE BAKERY. Health News **16**:204 (Dec. 11) 1939.

Eleven cases of violent gastroenteritis occurred in Troy, N. Y. The patients were found to have been infected through eating chocolate eclairs that had come from a single bakery. Investigation showed that one of the pastry cooks had a finger with a pustular discharge. Three other outbreaks have occurred in which this bakery was involved.

AIKMAN, Rochester, N. Y.

GASTROENTERITIS IN FREWSBURG DUE TO RAW MILK. Health News **16**:211 (Dec. 25) 1939.

In a village of 1,000 persons a number of cases of gastroenteritis were discovered. Investigation showed that all the milk had been obtained from the same raw milk dairy. It was found that a woman on one of the farms which furnished the milk had suffered from a gastrointestinal disturbance. She had not milked the cows but had assisted in washing the milk cans and pails.

AIKMAN, Rochester, N. Y.

SEROLOGICAL DIFFERENTIATION OF OBSTRUCTIVE FROM HEPATOGENOUS JAUNDICE BY FLOCCULATION OF CEPHALIN-CHOLESTEROL EMULSIONS. FRANKLIN M. HANGER, J. Clin. Investigation **18**:261 (May) 1939.

For this test, 1 cc. of an emulsion of sheep brain cephalin and cholesterol in distilled water is mixed with 0.2 cc. of blood serum in 4 cc. of physiologic solution of sodium chloride. The tube is thoroughly shaken and is then allowed to stand at room temperature twenty-four hours before notation of the flocculation and precipitation that may occur.

Of 900 samples of serum from normal persons, flocculation was observed in only 1. Twenty-five samples of serum from patients with obstructive jaundice (including patients with long-standing biliary obstruction with secondary fibrosis of the liver) gave negative reactions. Of 38 samples of serum from patients with jaundice due to hepatitis, catarrhal jaundice and cirrhosis, 33 gave prompt, strong flocculation reactions. In cases in which repeated tests were made, close correlation was demonstrable between the clinical severity of the disease and the degree of flocculation. Negative flocculation reactions were given by serums from some patients with jaundice appearing immediately after injections of arsphenamine.

The flocculation test as an index of disturbance of hepatic parenchyma does not parallel tests for hepatic function.

GUEST, Cincinnati.

BILIARY CIRRHOSIS. P. R. EVANS, Arch. Dis. Childhood **14**:89 (June) 1939.

Evans discusses the subject in detail, dividing biliary cirrhosis into four types:

1. Congenital biliary cirrhosis, with or without congenital obliteration of the bile ducts.

2. The infantile biliary cirrhosis of Indian nurslings, differing from congenital biliary cirrhosis in age incidence, local occurrence, slower course and absence of obliterative cholangitis.

3. Acquired obstructive biliary cirrhosis, of which the signs and symptoms are those of chronic, usually unremitting, obstruction of the common bile duct, enlargement of the liver and possibly of the spleen, sometimes portal failure and cholemia. Appropriate tests show impairment of liver function.

4. Acquired nonobstructive biliary cirrhosis (hypertrophic biliary cirrhosis, Hanot's syndrome), a rare disease of long duration, attacking mainly children and young adults. The onset is indistinguishable from catarrhal jaundice, but icterus does not completely disappear after the attack. Vomiting, epigastric pain and pyrexia subside, only to reappear at a later date. The course consists of a substratum of chronic jaundice and at first rather mild ill health, with exacerbations characterized by abdominal pain, pyrexia, increase in jaundice, enlargement of the liver and vomiting. The exacerbations recur at intervals of weeks or months and usually subside in two or three weeks but leave the patient in a poorer state than before. The spleen becomes palpable and in children may be enormous. The liver is at first likely to increase in size with each exacerbation. The stools vary, being usually pale and at times acholic. The urine contains bile salts and pigments. The van den Bergh reaction is biphasic. The blood picture is variable. Anemia may be macrocytic or microcytic but is frequently normocytic. There may be no anemia, and polycythemia is not unknown. Leukocytosis is common, but leukopenia occurs in a minority of cases. Tests of liver function show impairment.

KELLY, Milwaukee.

FAMILIAL HEPATITIS AND CHRONIC JAUNDICE. R. DEBRÉ, Proc. Roy. Soc. Med. **32**:1173 (July) 1939.

Debré reports the history of a family of 6 children, of whom 2, the eldest and the fifth, are normal; 3 died, a boy at 6 months of age and 2 girls at 9 and 10 years, respectively, from the same familial disease that has now attacked another

boy, aged 7. The essential features of this disease are hypertrophy of the liver and spleen, chronic icterus, with evidence of salts and bile pigments in the blood and urine and retardation of physical, mental and sexual development; slight deafness occurred in one of these patients and clubbing of the fingers in another. This condition is a good example of biliary cirrhosis of the liver.

After reviewing recent French observations, the author recalls the large contribution of English authors on the subject.

He then distinguishes three types of familial cirrhosis: (1) Laennec's type, with enlarged liver, (2) the splenomegalic anascitic and anicteric type, resembling Banti's syndrome, and (3) the commonest type, biliary cirrhosis.

The author describes particular histologic lesions, and when discussing differential diagnoses excludes dyslipoidic and polycoric cirrhosis and other forms of acquired cirrhosis in children. He then summarizes the relationships between this disease and the following conditions: (1) obstructive cirrhosis due to a congenital defect of the bile ducts, (2) cirrhosis in young Indians, (3) the syndrome of hepatic lenticular degeneration and (4) the syndrome of cirrhosis of the liver combined with hemangiomatosis. Finally, after recalling the close analogy of the condition with renal dwarfism, he shows how the interpretation of these relationships may throw light on the development of various progressive congenital diseases.

WILLIAMSON, New Orleans.

PYLORIC STENOSIS AND ITS TREATMENT. P. LEREBOULLET, Progrès méd., April 1, 1939, p. 450.

This discussion of pyloric stenosis adds nothing new. Lereboullet points out that the condition is found more frequently in England and the United States than in France and some other countries. This may be a matter of recognition, or it may be that the condition occurs more frequently in the Anglo-Saxon race. He is of the opinion that operation is the procedure of choice. Of his 40 patients who were operated on, only 1 died and the death of that patient could not be attributed directly to the operation.

LESLIE, Evanston, Ill.

POTASSIUM IN ACUTE GASTROENTERITIS. P. ROBINSON, Ann. pædiat. **153**:155 (June) 1939.

Robinson studied acute toxic gastroenteritis in 40 infants. The average value of potassium in the serum was 10.9 mg. per hundred cubic centimeters compared with 19 mg. for healthy children. This decrease is not due to loss of potassium but to wandering of potassium from the serum into the cells. The prognosis depends on the amount of potassium in the serum. A low value means a bad prognosis; a high value, a good one. Basing his opinion on the electrophysiologic theory of permeability, Robinson considers the increase of potassium in the cells a consequence of their exsiccation and the quantity of potassium as an indicator of the degree of the cellular exsiccation. In cases of toxic dysentery he found an increase of potassium in the serum.

FROM AUTHOR'S SUMMARY.

OBSTRUCTION OF THE INTESTINE BY A NEUROGLIOMA IN AN INFANT. O. SAXL, Ann. pædiat. **153**:166 (June) 1939.

A baby of 6 weeks began to be constipated. Not much attention was paid to this symptom in the beginning. It became gradually more pronounced. After a month there were signs of ileus and anuria, also venous congestion and paresis of the lower extremities. On admission of the infant to the hospital there was suspicion that a tumor was the cause of these symptoms. Rectal examination confirmed the diagnosis. A roentgen picture of the abdomen revealed a tumor of the right sacral bone. An operation could not be performed on account of the serious condition of the patient. Death ensued after two days' residence in the hospital.

The importance of an exact clinical invesigation, including rectal examination, in cases of persistent constipation in infancy is pointed out. If this should not give an absolutely negative result, roentgen examination is necessary.

FROM AUTHOR'S SUMMARY.

CLINICAL PICTURE OF ACUTE YELLOW ATROPHY OF THE LIVER IN CHILDHOOD. V. RATZKOWSKI, Ann. pædiat. **154**:40 (Oct.) 1939.

After a short survey regarding the frequency of acute yellow atrophy in infancy, 2 fatal cases of acute breakdown of the liver are reported. One patient was a child of 5 and the other a child of 8 years. In one case the hepatic disease was a rare complication of pneumonia; in the other it started in the course of hepatocellular jaundice. The possibility of allergic influences in this case is discussed.

FROM AUTHOR'S SUMMARY.

GALLSTONES IN CHILDREN. E. MELCHIOR, Ann. pædiat. **154**:292 (Feb.) 1940.

Attention is again directed to the fact that cholelithiasis occurs in childhood with the same chances of complications as in adult life. For this reason it must be carefully regarded by the pediatrician as well as by the surgeon.

FROM AUTHOR'S SUMMARY.

DIAGNOSIS OF ACUTE APPENDICITIS IN CHILDHOOD. H. KOCH, Wien. klin. Wchnschr. **36**:836 (Sept. 8) 1939.

Koch notes that in the early stage of appendicitis, if the classic symptoms are not yet marked, tension of the abdominal wall is frequently evident on the right side. However, this tension can be felt only on very gentle palpation with the finger tips.

If peritonitis has already set in, the skin over the abdomen feels slightly edematous; often this fact can be detected only by comparison with the skin of the chest. In these cases the boundary between the normal skin over the chest and the edematous skin of the abdomen can be plainly felt at the site of insertion of the diaphragm.

ABT, Chicago.

CIRRHOSIS OF THE LIVER IN CHILDHOOD. R. PRIESEL and F. SCHULER, Wien. klin. Wchnschr. **36**:840 (Sept. 8) 1939.

Twenty-two cases of cirrhosis of the liver in childhood, 11 of which were personally observed, are reported by Priesel and Schuler. There were 8 girls and 14 boys in the series, none of them over 2 years old; in fact, 16 were only about 1 year old. They all lived in the same vicinity.

The onset was insidious and manifested itself in lassitude, failure to gain and loss of appetite. The limbs were thin, but the abdomen was so enlarged that the afflicted child could not sit. Pressure on the abdomen was painful. The liver and spleen could often be felt below the ribs. As the disease developed, icterus appeared, and the stools became acholic. During the entire illness there was fever, varying between 38 and 40 C. (100.4 and 104 F.). In the terminal stage the patient often vomited bile and blood and had nosebleed. Anemia and leukocytosis were invariably present. In 12 of the cases reported there was caput medusae.

The prognosis for cirrhosis of the liver in early life is extremely bad. Death usually occurs in a few months. Occasionally, a patient survives; a child in the authors' series was alive two years after onset, but the abdomen was still distended.

Alcohol was definitely not the cause in any of the cases reported here. Tuberculin tests were negative. Autopsy in 2 cases revealed interstitial syphilitic hepatitis, indicating that the disease was possibly due to syphilis. No connection with typhus or paratyphus could be traced, and hepatitis epidemica in such young patients is improbable. The authors believe that an infection by some unknown

agent must be responsible; this would account for the regional incidence reported here and also for the fever and leukocytosis. A familial tendency may also be indicated by the fact that twin siblings of one of the patients had died of jaundice. Gleirscher has reported that 4 children of one brother and 3 of another died of "liver cirrhosis."

ABT, Chicago.

PASSAGE OF AIR THROUGH THE DIGESTIVE TRACT OF INFANTS. V. SOVERI, Acta pædiat. (supp. 3) **23**:1, 1939.

Following a prefatory, well documented review of the relevant literature, Soveri reports the results of his own investigations into the genesis of meteorism in infants. The subjects were all under 12 months of age. The experiments consisted of roentgenographic observation of the passage of gas through the alimentary tract, sometimes with the aid of small amounts of opaque medium. Among others, the following generalizations are recorded:

Empty suckling, i. e., sucking a nipple that is not attached to a bottle containing fluid, does not introduce an appreciable amount of gas into the stomach. On the other hand, suckling that results in the deglutition of less fluid than the infant can comfortably swallow in any one act does result in the passage of a large volume of gas into the stomach. In other words, when a bottle is emptied slowly and lazily, more air is swallowed than when it is consumed rapidly.

Air disappears from the stomach with great rapidity; even large amounts vanish within thirty minutes. In consequence of this fact, the stomach that contains no food is always free of gas. In general, air disappears from the stomach synchronously with fluid, although occasionally it may remain longer than food. The intestines show a tendency to retain air, so that in fully half of the cases this region may not be airless after twelve to fourteen hours of fasting. The large intestine retains air longer than the small intestine. Physical activity is the most important of the factors that contribute to the evacuation of the intestines. If the small intestine is free of food, air passes rapidly into the colon. It remains in this viscus so long that the large intestine can be regarded as a storehouse for gas as well as for fecal material.

McCUNE, New York.

EPIDEMIC AND SPORADIC ICTERUS: A STATISTICAL EPIDEMIOLOGIC AND CLINICAL INVESTIGATION. P. SELANDER, Acta pædiat. (supp. 4) **23**:3, 1939.

The formal purpose of Selander in this 250 page monograph is to determine whether or not the same agent is responsible for the two types of infectional jaundice referred to in the title. Since it is still not possible to attack the problem bacteriologically, an oblique approach was necessarily pursued. An analysis of data relating to 1,200 cases of jaundice, originating principally in Göteborg and Gotland, revealed, among others, the following facts: In general, both diseases show a predilection for children between 2 and 15 years of age; both are more common in urban communities than in the country; both reach a peak of frequency in October and November and a minimum in June and July; from the points of view of symptomatology and complications the diseases show close resemblance. The only important difference between the two types of jaundice lies in the fact that in some cases of sporadic icterus there appears to be an incubation period of from two to three months, a feature which appears incompatible with capacity to give rise to a fulminating epidemic. The 10 pages of bibliography will be helpful to any one interested in reviewing the subject first hand.

McCUNE, New York.

ACUTE CHOLECYSTITIS IN CHILDHOOD. C. VAN STAVEREN, Nederl. tijdschr. v. geneesk. **83**:4115 (Aug. 19) 1939.

Acute cholecystitis was observed in a boy 7 years old. Studies of the recent literature show this disease to be more common in childhood than had been believed.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF JAUNDICE WITH INSULIN AND A DIET RICH IN CARBOHYDRATES. H. J. M. VAN PANTHALEON VAN ECK, Nederl. tijdschr. v. geneesk. **93**:5160 (Oct. 28) 1939.

No value is attached to the clinical evidence for giving insulin together with carbohydrates in cases of disturbed liver function. In view of personal experiments insulin is assumed to have an unfavorable effect on the glycogenic capacity of the normal and the diseased liver. The insulin-dextrose treatment of jaundice is considered scientifically unjustifiable. The administration of carbohydrates alone, in large quantities and, if possible, orally is recommended.

VAN CREVELD, Amsterdam, Netherlands.

## Nervous Diseases

SULFANILAMIDE AND MENINGITIS. S. W. SAPPINGTON and GRANT O. FAVORITE, Ann. Int. Med. **13**:576 (Oct.) 1939.

The cases of 227 patients with meningitis are reviewed. Those in which the hemolytic streptococcus and the meningococcus were the causative organisms responded best to sulfanilamide therapy. The results in cases of pneumococcic meningitis were better than with previous types of treatment employed. Sulfanilamide had little or no effect in influencing the course of influenzal and tuberculous meningitis.

READING, Galveston, Texas.

DISSEMINATED ENCEPHALOMYELITIS. TRACY J. PUTNAM and LEO ALEXANDER, Arch. Neurol. & Psychiat. **41**:1087 (June) 1939.

The authors give an excellent description and classification of encephalitis and a detailed pathologic description of a group of cases in which there was disseminated inflammation secondary to multiple thrombi.

BEVERLY, Chicago.

RECOVERY FROM APHASIA STUDIED IN CASES OF LOBECTOMY. J. M. NIELSEN and R. B. RANEY, Arch. Neurol. & Psychiat. **42**:189 (Aug.) 1939.

Three new cases in which aphasia was studied after "major left temporal lobectomy," performed surgically in 2 instances and by nature (thrombotic softening) in 1, and 1 case of "minor right temporal lobectomy" are reported. The results seem to indicate that recovery of control of language is greater in patients with complete loss of the major temporal lobe than in those with mere damage to it. There is also evidence to indicate that the minor temporal lobe may have considerable function in language.

BEVERLY, Chicago.

STREPTOCOCCIC OTITIC MENINGITIS. MORRIS A. WEINSTEIN, Arch. Pediat. **56**: 508 (Aug.) 1939.

Three cases are reported, with 1 recovery. The treatment is outlined.

ORR, Buffalo.

HYDROCEPHALUS FOLLOWING SUBARACHNOID HEMORRHAGE. H. R. MERWARTH and I. S. FREIMAN, Brooklyn Hosp. J. **1**:149 (July) 1939.

A case is presented in which a spontaneous subarachnoid hemorrhage in a child 5 weeks of age was followed by the gradual development of hydrocephalus.

Subsequent examination of the brain revealed as the source of bleeding a small telangiectatic angioma situated in the thalamic region.

Widespread thickening and adhesions of the pia and arachnoid were demonstrated and were interpreted as the result of the hemorrhage and the cause of the hydrocephalus, which was of the "communicating" type.

Treatment of subarachnoid hemorrhage by frequent lumbar puncture is recommended both for its immediate therapeutic effect and as prophylaxis against the potential complication, hydrocephalus. FROM THE AUTHORS' SUMMARY.

THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH SULFANILAMIDE. BARBARA A. HEWELL and A. GRAEME MITCHELL, J. A. M. A. **112**:1033 (March 18) 1939.

The authors report that before sulfanilamide was used all the patients in a series of 23 cases of pneumococcic meningitis died. Since the use of sulfanilamide or of related compounds was begun, at least 30 recoveries are known of, and the authors add 3 from their 6 cases in which the drug was used. The results show a definite beneficial effect of this type of chemotherapy.

HEERSMA, Kalamazoo, Mich.

COCCIDIOIDAL GRANULOMA SIMULATING BRAIN TUMOR IN A CHILD OF FOUR YEARS. B. P. STORTS, J. A. M. A. **112**:1334 (April 8) 1939.

A case is reported.

HEERSMA, Kalamazoo, Mich.

PERIPHERAL NEURITIS: ALLERGY TO HONEY BEE STINGS. ALEXANDER T. ROSS, J. Allergy **10**:382 (May) 1939.

A case of peripheral neuritis involving the right radial, median, ulnar and dorsal antibrachial cutaneous nerves is reported. The patient was an apiarist and had been stung frequently for several years, with only slight reaction. Repeated stings on the right arm, left arm, chest and legs produced swelling, weakness and numbness of the right hand and generalized symptoms. The sensory changes lasted for a week and weakness of the muscles for two weeks.

HOYER, Cincinnati.

MENINGITIS DUE TO MICROCOCCUS TETRAGENUS. MODESTINO CRISCITIELLO JR., New England J. Med. **221**:383 (Sept. 7) 1939.

The case of an 18 year old white youth is reported in detail. Sulfanilamide apparently was a factor in recovery.

A perusal of the literature brings out the fact that Micrococcus tetragenus is rarely found as the cause of meningitis. This organism is ordinarily found in the nose and throat, where it is not considered pathogenic. Although this patient gave no history of infection of the upper respiratory tract, it is likely that the organism gained entrance to the central nervous system from the right ethmoid sinus.

GENGENBACH, Denver.

RESULTS OF TREATMENT OF IDIOPATHIC EPILEPSY BY COBRA VENOM. A. BARBEAU and E. LAURENDEAU, Union méd. du Canada **68**:363 (April) 1939.

Six children aged 13 to 17 years who had had epilepsy for one to eleven years were given cobra venom. The authors present their preliminary findings, with an apology for their incomplete reports. The frequency of attacks seemed to decrease, the number of days without attacks increased and the attacks themselves seemed less severe.

DAFFINEE, Boston.

A CASE OF STREPTOCOCCUS MENINGITIS OF OTOGENIC ORIGIN WITH RECOVERY. ALLEN T. HAWTHORNE, Virginia M. Monthly **66**:267 (May) 1939.

A child aged 8 years had bilateral otitis media followed by spontaneous rupture of both eardrums. When seen by the author, four weeks after the onset, the right ear was still draining and the smear showed short chain streptococci. Twenty-four hours later meningitis had developed. Roentgen examination revealed acute mastoiditis with destruction of all cells. The spinal fluid showed a short

chain streptococcus. The child was extremely ill but, after 10 grains (0.65 Gm.) of sulfanilamide every four hours had been given for forty-eight hours, appeared symptomatically almost well. Twelve days after the onset of meningitis, without having had any operation, he was entirely well of both meningitis and mastoiditis.

STONE, Richmond, Va.

NEUROLOGY—SOME MODERN PROBLEMS. W. RITCHIE RUSSELL, Edinburgh M. J. **46**:221 (April) 1939.

The author briefly discusses deficiency diseases, neurosyphilis, disseminated sclerosis and epilepsy, all from the recent aspects, particularly the transmission of nervous impulses dependent on liberation of a chemical substance. He thinks that there is some evidence to prove that acetylcholine is the substance concerned with transmission of nervous impulses in the brain and spinal cord. A chemical substance may be associated with faulty liberation, causing the muscular condition known as myotonia, a state in which the myotonic muscle contracts strongly but relaxes slowly. Wolff has reported in the last few years that quinine relieves myotonia but has a bad effect on neurasthenia gravis. Russell confirms this.

The question of rhythm is suggested by recurrence in certain cases of epileptic fits at certain hours only of the day or night and in other cases only during sleep, while falling asleep or after waking. The combination of a fit and a violent discharge in the brain appears to allow the brain to return to normal for an interval by giving a temporary immunity. This transmission of nervous impulses at the cerebral cortex is probably as much dependent on a chemical substance as is the aforementioned transmission in myotonia. The normal activity at the cortex is concerned with an excessive liberation of the chemical transmitter. There may be something analogous between myotonia and epilepsy; mental activity is known to lessen the likelihood of a fit, and exercise of the muscles in a case of myotonia tends to make the physiologic muscular state of the patient more nearly normal. Grand mal seizures have been correctly predicted by electroencephalographic tracings on the morning of the days the fits occurred, as reported by Gibbs and his co-workers, who designated the phenomenon as evidence of pathologic physiology in epilepsy. It is hoped that such new methods in the study of epilepsy will increase physicians' knowledge of the physiology of the brain as well as its treatment.

NEFF, Kansas City, Mo.

THE MICROGLIA. PIO DEL RIO-HORTEGA, Lancet **1**:1023 (May 6) 1939.

Nerve tissue contains cells with properties corresponding to those of the reticuloendothelial system. The chief function of these cells (the microglia) is the phagocytosis of waste products and, if need be, of red blood cells.

Even when they are in apparent rest, microglia cells remain capable of migration, and under pathologic conditions they are mobilized to undertake phagocytic activity. Phagocytosis in nerve centers is a specific function of microglia; despite opinions to the contrary, neither the astrocytes nor the oligodendrocytes take part in it.

LANGMANN, New York.

JAW-WINKING IN AN INFANT. J. N. O'REILLY, Proc. Roy. Soc. Med. **32**:607 (April) 1939.

The case of a boy aged 6 months is reported. Movements of the left eyelid coordinated with sucking movements of the jaw had been noticed since birth. There was no history of trauma at birth. On examination there was a considerable degree of ptosis on the left side. Sucking movements caused elevation of the left upper lid, which was otherwise motionless. The right side appeared normal.

WILLIAMSON, New Orleans.

SUBARACHNOID HAEMORRHAGE. E. A. COCKAYNE, Proc. Roy. Soc. Med. **32**:1173 (July) 1939.

The case of a girl 11 months old is reported. She had suffered for a week with transitory attacks of vomiting, pallor and limpness before her admission to the hospital. On examination she was comatose and the fontanel was bulging. Flexion of the neck was not resisted but produced flexion of the hips. Profuse retinal hemorrhages in both fundi and many subhyaloid hemorrhages were present. There was no swelling of the disks. The pressure of the cerebrospinal fluid was 300 mm., and the fluid was densely blood stained. The day after admission the child had a "fit" on the right side lasting a few hours. During this seizure the cerebrospinal fluid was found to be less blood stained than before. From that time the child made an uneventful recovery. She appeared perfectly well when last seen. The cerebrospinal fluid nine days after admission was only slightly blood stained. The Wassermann reaction of the fluid was negative. The bleeding and coagulation time were normal, as was the full blood count.

WILLIAMSON, New Orleans.

TUMOR OF THE CEREBELLAR VERMIS CLINICALLY SIMULATING AN ENCEPHALITIC PROCESS. FILIPPO DE LUCA, Med. ital. **17**: 53 (Feb. 28) 1939.

The author presents the case of a child 2½ years old who fifteen days before entrance into the hospital presented a clinical picture characterized by: irregular intermittent fever; exhausting nervous vomiting; increasing headache, most frequently occipital but sometimes frontal; generalized tonic-clonic convulsions; nuchal rigidity with hyperextension of the head; moderate mental torpor; papilledema; slight muscular weakness on the left, more marked in the lower extremity, and slight cerebellar ataxia. Lumbar puncture showed increased pressure and an increased sugar content but revealed otherwise normal conditions. On the eighth day the patient showed marked opisthotonos and died suddenly without appreciable signs.

The author discusses the significance and differential diagnosis of each one of the "positive findings" in arriving at the diagnosis of cerebellar tumor of the vermis. Differentiation between cerebellar tumor and encephalitis is discussed. A discussion as to the location of the tumor and the type of lesion is presented.

Autopsy showed a glioma of the cerebellar vermis. MARTOCCIO, Utica, N.Y.

TUMOR OF THE CEREBELLUM AND OF THE FOURTH VENTRICLE IN CHILDREN. S. LEVI, Riv. di clin. pediat. **37**:230 (March) 1939.

On the basis of 35 cases seen in the pediatric clinic in Florence, Italy, Levi reviews the diagnostic importance of each of the signs and symptoms of cerebellar tumor.

HIGGINS, Boston.

ETIOLOGY OF BENIGN LYMPHOCYTIC MENINGITIS; A CASE OF DIPLOCOCCIC CAUSATION. O. MALAGUZZI-VALERI, Riv. di clin. pediat. **37**:520 (June) 1939.

A nursing infant aged 5 months suddenly showed symptoms of meningitis. Lumbar puncture yielded ground glass fluid. Three per cent of the cells were polymorphonuclears and the remainder were lymphocytes and large mononuclears. The value for sugar was 0.55 per cent. No organisms were obtained on smear; pneumococci type I were obtained on culture. Antimeningococcus serum was given. The child recovered quickly. Three months later a similar attack occurred, but no organisms were recovered.

The pneumococci must have had an attenuated virulence. Benign lymphocytic meningitis may not always have a specific cause, nor is it always due to a virus infection.

HIGGINS, Boston.

A Case of Postencephalitic Contractures. P. Poletti, Riv. di clin. pediat. **37**:673 (Aug.) 1939.

A boy aged 12 years had acute encephalitis at the age of 4 years. At 7 years he began to have difficulty in walking; flexor contractures of all his limbs gradually developed. He also showed precocious sexual development.

Higgins, Boston.

Purulent Meningitis in an Infant Treated with Sulfapyridine. G. Gomez del Rio and B. Sanchez Santiago, Arch. de med. inf. **8**:234 (Sept.) 1939.

After a digestive disturbance meningitis developed in a 6 month old child, caused by a bacterium of the escherichia type, which was recovered from the spinal fluid. The child recovered following oral administration of 0.75 Gm. of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), 1.5 Gm. per 20 pounds (9 Kg.) of body weight.

Sanford, Chicago.

Operation for Cerebral Abscess. C. Urrutia U., Rev. chilena de pediat. **10**: 474 (Aug.) 1939.

This case report concerns a child 5 years old in whom an extensive abscess developed in the frontal lobe, following bilateral purulent otitis media of several months' duration.

Encephalographic examination proved to be the most valuable diagnostic procedure. The abscess involved almost the entire frontal lobes.

It was drained with the region under local anesthesia. Death shortly followed the operation and was preceded by extreme hyperpyrexia. The hyperpyrexia was due, the author believes, to reabsorption of septic products and their effect on the heat center.

Schlutz, Chicago.

Encephalography in Childhood. W. Brenner, Ztschr. f. Kinderh. **60**:595 (April 1) 1939.

The indications, the method of examination and the roentgen technic are discussed. Excellent roentgenograms are shown. The author describes the results of encephalographic procedures in numerous cases and in some instances compares his results with those of other authors. The findings for *"Balkenmangel"* are stressed. In some cases these findings have been interpreted erroneously as indicating a cyst. In cases of jacksonian epilepsy, encephalography is a valuable diagnostic aid, making successful surgical treatment possible.

Siemsen, Chicago.

## Diseases of the Genitourinary Tract

The Treatment of Cryptorchidism with Gonadotropic Substance. Carl Zelson, J. Pediat. **14**:452 (April) 1939.

Twenty-six cryptorchid boys were treated with the gonadotropic principle obtained from the urine of pregnant women (follutein). Each boy was given 3 to 6 injections a week for a period ranging from two weeks to fourteen months. The total dose varied between 1,350 and 39,100 units. The injections were given intramuscularly, and the size of a single dose varied from 100 to 1,000 units. In 18 cases the condition was unilateral and in 8, bilateral. Complete descent occurred in 8 cases (31.0 per cent). In 5 the condition was unilateral, and in 3, bilateral. Six of the 8 successfully treated patients were children under 10 years of age. Reports in the literature also show the most successful results in the cases of children under the age of 10 years, and for this reason Zelson feels that treatment should be seriously considered for children in the earlier age groups.

Rauh, Cincinnati.

URINARY INFECTIONS IN INFANTS AND CHILDREN (A COMPARISON OF THERAPEUTIC METHODS). BENJAMIN W. CAREY JR., New York State J. Med. **39**:685 (April 1) 1939.

If the infection is the first attack, medical treatment may be instituted without complete study, but if there is evidence of impaired renal function or of an anomaly of the bladder or urethra, cystoscopic examination is indicated. When the infection occurs repeatedly, the examination should be complete. Mandelic acid was given to 40 children and sulfanilamide to 41. Ten per cent elixir of ammonium mandelate was given in amounts necessary to keep a 1 per cent concentration in the urine. The acidity of the urine was checked daily to ascertain whether the $p_H$ was at the level of 5.6 or below. In general, sulfanilamide gave the better results. Objections to the use of mandelic acid are based on the presence of fever, vomiting or acidosis, diminution of renal function (to such an extent that concentration of the urine to a specific gravity of 1.020 is impossible) and infection due to Bacillus proteus.

AIKMAN, Rochester, N. Y.

TREATMENT OF GONORRHEA IN THE FEMALE AND OF VULVO-VAGINITIS IN LITTLE GIRLS. GLADYS M. SANDES, Practitioner **143**:157 (Aug.) 1939.

There are, in the main, two groups of children who show gonococci in their vaginal smears: (*a*) those infected at birth from direct contact with the mother's vaginal discharge and (*b*) those infected later either by assault (which is relatively rare) or by infected linen or towels contaminated by discharge from an infected person.

Children infected at birth may have some discharge soon after birth, or (more usually, owing to the normal vaginal secretion at that time) the signs may not appear for some weeks. Such infants require little treatment except frequent baths and occasional vaginal swab-outs with 10 per cent strong protein silver U. S. P. and glycerin or some similar solution.

Children infected later are best treated by increasing their natural resistance to the infection and by a minimum of local treatment. It is only fair to say that this view is not held by all workers in this field. The child should be in bed for the first week or two or until the acute stage of the vulvovaginitis has passed. During this period, and subsequently, baths should be given three times daily. No antiseptic need be used. Later, if swab-outs are necessary the solutions used should be only half the strength of those used for the adult. Douching is rarely required. The child is given a diet rich in vitamin, and in winter general ultraviolet irradiation is of great value. Administration of vaccines may be helpful in a case of refractory involvement.

As a test of cure, three sets of smears taken at monthly intervals after all treatment has been completed together with a negative gonococcic fixation reaction are essential. The last set of smears should be taken after a provocative injection of 0.25 cc. of gonococcic vaccine and should not show pus cells or organisms. It may take several months to accomplish this.

GELSTON, San Francisco.

VARIETIES OF RENAL DWARFISM. L. CAUSSADE, M. VERAIN and N. NEIMANN, Arch. de méd. d. enf. **43**:65 (March-April) 1940.

The coexistence of chronic nephritis with disorders of development was noted fifty years ago by Lancereaux, but it remained for English authors (Goodhart, Lucas and others) to establish the syndrome of renal dwarfism as a distinct entity. The present contributors divide the cases into three categories: (1) the pure type as commonly understood, (2) the form associated with osteoclastic rickets and (3) the variety complicated by hemolytic icterus.

A total of about 120 cases have been reported, to which the authors add 3 more, illustrating the several classifications described. The clinical signs common

to all groups include an early arrest of growth with corresponding deficiencies in weight and stature, going on to true dwarfism. In about 30 per cent of the children afflicted, severe, deforming rickets of the delayed or late type is found, with particular emphasis on the lower limbs. The arms, the chest and the skull are usually spared. Rachitis may be so discrete that roentgenograms alone can facilitate the diagnosis. In older children, dwarfism is accompanied by infantilism.

The renal manifestations constitute the most significant feature of the syndrome; there exists a chronic form of nephritis characterized by polyuria, albuminuria, cylindruria and especially elevated azotemia, the nitrogenous content of the blood frequently amounting to 1 Gm. per liter. It is unusual in type on account of its latency and the utter absence of known etiologic factors. Slight infections or perhaps some orthopedic intervention may activate this latent stage ino a formidable assault, with high nitrogen retention and uremic coma. An imperious thirst, resembling that of diabetes insipidus, is universally found to accompany the polyuria. Death usually ensues before puberty.

AMESSE, Denver.

DWARFISM WITH RENAL RICKETS: A CASE REPORT. GRENET, GAUTHERON and SAULNIER, Arch. de méd. d. enf. **43**:82 (March-April) 1940.

The authors discuss in detail the clinical history of a girl of 14 years exhibiting the characteristic syndrome of renal rickets. There was a striking arrest of development, the patient showing the weight and measurements of a child of 9, while the osseous deformity (genu valgum) was so pronounced that she was unable to walk.

Examination of the blood revealed hypocalcemia and hypophosphatemia; infantilism was marked, and the urine contained albumin in small quantities, without pus or casts. Pyelograms showed atrophy of the bladder and bilateral dilatation of the ureters with absence of the right inferior calix. Typical roentgenologic evidences of rickets were not found until the age of 13.

AMESSE, Denver.

PARAURETHRAL GLANDS AND FOLLICLES IN THE NEWBORN. G. MONTELLA, Pediatria **47**:490 (June) 1939.

The urethras from 14 newborn infants were examined microscopically in stained sections. The structure and location of the glands and follicles are described. The glands were found to be more numerous on the dorsal surface of the urethra and were found also in the glans.

MARTOCCIO, Utica, N. Y.

AN UNUSUAL CASE OF CONGENITAL URETHRAL STENOSIS. L. FRANZI, Pediatria **47**:506 (June) 1939.

Franzi presents the pathologic observations in congenital urethral stenosis in a premature infant aged 8 days. Autopsy showed stenosis of the membranous portion of the urethra with dilatation and hypertrophy of the bladder, dilatation and lengthening of both ureters and hydronephrosis of the right kidney.

MARTOCCIO, Utica, N. Y..

## Diseases of the Ductless Glands; Endocrinology

A NEW MATHEMATICAL METHOD FOR THE EVALUATION OF ENDOGENOUS INSULIN SECRETION. M. M. MILLER and O. P. ALLEN, Ann. Int. Med. **13**:636 (Oct.) 1939.

Basing their studies on Hartmann's calculation for the insulin requirement, Miller and Allen show how from actual changes in the blood sugar one may estimate the amount of endogenous insulin being supplied and so have a more accurate gage for the amount of exogenous insulin required. This is possible only after a sufficient number of calculations have been made to strike an average and

after the patient has become somewhat stabilized. During coma a failure of the blood sugar to drop an expected amount, in accordance with the conception that 1 unit of insulin will take care of 2 Gm. of dextrose, indicates primarily, the authors feel, a failure of the mechanism for storing glycogen. They do not take into account that there may be a continuation of the breaking down of body protein during this period.

The study is stimulating and of definite practical interest. For the details of calculation, the original article should be consulted. LESLIE, Evanston, Ill.

INFLUENCE OF ULTRAVIOLET IRRADIATION UPON EXCRETION OF SEX HORMONES IN THE MALE. ABRAHAM MYERSON and RUDOLPH NEUSTADT, Endocrinology **25**:7 (July) 1939.

Irradiation of men with the mercury quartz lamp was found to increase excretion of androgen in the urine, particularly when the scrotum was irradiated. These experiments gave no evidence that the pituitary plays a primary role in the stimulation of increased androgenic activity. JACOBSEN, Buffalo.

RELATION BETWEEN THE GROWTH PROMOTING EFFECTS OF THE PITUITARY AND THE THYROID HORMONE. HERBERT M. EVANS, MIRIAM E. SIMPSON and RICHARD I. PENCHARZ, Endocrinology **25**:175 (Aug.) 1939.

Experiments with normal, thyroidectomized and thyroidectomized and hypophysectomized rats showed that growth promotion secured by administration of anterior pituitary extracts is not dependent on the presence of the thyroid but is greater when the thyroid is present or when thyroxin is concomitantly administered. JACOBSEN, Buffalo.

FURTHER STUDIES ON THE ANTAGONIST TO ADRENALIN HYPERGLYCEMIA IN PITUITARY EXTRACTS. A. H. NEUFELD and J. B. COLLIP, Endocrinology **25**:775 (Nov.) 1939.

Evidence has been presented to show that certain preparations of posterior pituitary when administered to mice, rats, rabbits monkeys and a dog acted in antagonism to hyperglycemia induced with epinephrine. The evidence available does not indicate a relation of this substance to other well known pituitary principles. JACOBSEN, Buffalo.

ENDOCRINE DYSCRASIAS ASSOCIATED WITH CONDUCT DISORDERS IN COLORADO SPRINGS CHILDREN. C. S. GYDESEN and B. J. MURPHEY, Rocky Mountain M. J. **36**:462 (July) 1939.

In view of the contradictory and confusing reports regarding the relationship or lack of relationship between behavior disorders in children and the various endocrine dyscrasias, Gydesen and Murphey reviewed 64 cases in which children had been examined by a psychiatrist in a child guidance clinic and also by an endocrinologist in private practice. Thirty-six of the children were referred to the endocrinologist by the child guidance clinic as presenting a possible endocrine dyscrasia. The 36 cases were selected from a series of 313 consecutive cases in which the children were fully studied at the child guidance clinic. Disorders of the thyroid (32 cases) and pituitary gland (18 cases) were by far the most common conditions discovered. All the children treated specifically showed definite improvement in their school and social adjustment. J. A. M. A.

THYMUS FUNCTION. R. TURPIN, Union méd. du Canada **68**:705 (July) 1939.

Turpin's studies, with white rats as subjects, gave results not entirely in accord with other reports. Thymectomy seemed to have no effect on growth up to the

eighth generation. Fertility did not seem to be affected. Thymectomized animals matured at an earlier age than did normal animals. Prepubertal development was modified temporarily, but the hypertrophy thus produced had disappeared at three months. Glutathione metabolism is involved through thymectomy; Turpin's observations in this respect are comparable to those of Binet in dogs which had undergone extirpation of the pancreas, ovaries, hypophysis or parathyroids.

DAFFINEE, Boston.

EFFECT OF ESTROGENIC HORMONE ON THE PROSTATE OF THE MARSUPIAL TRICHOSURUS VULPECULA. A. CARRODUS and A. BOLLIGER, M. J. Australia **2**:633 (Oct. 28) 1939.

Ten opossums of varying ages were given weekly intramuscular injections of different doses of an estrogenic substance. All experiments terminated fatally. Experiments in which a short survival period occurred were characterized by toxic changes in the renal parenchyma. In the experiments with a longer survival period hydroureters and hydronephrosis developed in 6 animals; 2 showed in addition, vesical calculi. The prostate was not increased in size in any of the experiments; on the contrary, it was small. The histologic changes observed in the prostate gland included fibrosis, most marked around the urethra, and epithelial changes, such as hyperplasia, metaplasia and keratinization; in one experiment an intraurethral papilloma developed.

GONCE JR., Madison, Wis.

MENTAL DEVELOPMENT IN CONGENITAL MYXEDEMA. L. F. SCHAEFFER, Acta pædiat. **23**:434, 1939.

During the last twenty years 28 patients with congenital myxedema have been recognized in the University Children's Clinic, Amsterdam. Of these, 3 are not available for follow-up purposes and 5 have died. The single autopsy was uninformative. Twenty patients have recently submitted to follow-up examination. The present report concerns itself exclusively with data relating to their mental development.

Eight of the patients were tested by the technic described by Bühler and Hetzer; this takes account of sensory perception, physical agility, social behavior, docility, constructive ability and intellectual creativeness. By this method the average attainment of the members of the group, expressed as intelligence or development quotients, varied between 30 and 130. However, with a single exception the members of the group showed deficiency in the equilibratory tests, particularly those involving static equilibrium, which served to demarcate them from children with other types of mental defect. Other psychometric tests employed were the Binet-Simon, the Pinter-Cunningham and the Oseretzky. The median intelligence quotient for 22 patients lay between 60 and 70, with extremes at 25 and 130. It was apparent that the severest conditions became manifest soonest after birth. Although there was some indication that the character of the outcome was influenced by the time at which treatment was instituted, outstanding exceptions to this generalization were apparent. The doses of thyroid that were used seem small.

MCCUNE, New York.

FIVE YEARS' EXPERIENCE WITH "FREE DIET" IN CHILDHOOD DIABETES. A. LICHTENSTEIN, Acta pædiat. **24**:171, 1939.

Stolte's principle has now been applied to the treatment of between 50 and 60 juvenile diabetic patients receiving treatment at the Crown Princess Louisa's Children's Hospital, Stockholm. Complete freedom of diet is permitted; no attention is paid to glycosuria. Ketosis and insulin shock are carefully avoided. The results have been most gratifying. In summary: Not a single patient is on a diet; the general state of the children is excellent; all have grown normally; a few

have become moderately overweight; several have passed through puberty without difficulties of any sort; their resistance against infection is excellent; the incidence of coma has been much reduced, and no tendency toward arteriosclerosis has been recognized. Since the introduction of the newer compounds of insulin the majority of patients require only a single injection daily. The daily dose of insulin varies between 20 and 100 units.

McCUNE, New York.

PLASMA CHOLESTEROL, ELECTROCARDIOGRAM AND BLOOD PRESSURE IN CHILDREN WITH DIABETES TREATED WITH "FREE DIET." F. KARLSTRÖM, Acta pædiat. **24**:177, 1939.

This investigation is based on the ample clinical material provided by the 50 juvenile diabetic patients treated without restriction of diet under the supervision of the Crown Princess Louisa's Children's Hospital, Stockholm. Seventy-eight analyses in 35 cases showed plasma cholesterol elevated in children with diabetes: Whereas the mean concentration of cholesterol in the plasma of healthy children was 169 mg. per hundred cubic centimeters, that of the diabetic children was 226. The concentration of cholesterol bore no evident relation to the degree of hyperglycemia nor to the degree of ketosis in those patients who were thought to be in satisfactory condition. Electrocardiographic examination of 38 patients yielded abnormal tracings for 7; in 5 of these patients no cause other than diabetes could be found to account for the peculiarities. The abnormalities were of trivial character. A slight elevation of the mean blood pressure of the diabetic children is ascribed to emotional causes. None of the children showed signs of cataract. Roentgen examination of the hands and feet of those patients who had suffered from diabetes for more than three years failed to reveal evidence of calcification of the arteries.

McCUNE, New York.

DIABETES AND RETARDATION OF GROWTH IN CHILDREN WITH AND WITHOUT ENLARGEMENT OF THE LIVER. C. E. RÄIHÄ, Acta pædiat. **24**:184, 1939.

Four cases of juvenile diabetes are reported in which disturbance of growth was a conspicuous feature; in 2 of the cases the liver was greatly enlarged. Evidence is produced to strengthen the arguments for the involvement of the hypophysis cerebri in the genesis of human diabetes.

McCUNE, New York.

DIABETES MELLITUS WITH RETARDATION OF GROWTH AND ENLARGEMENT OF THE LIVER. A. SUNDAL, Acta pædiat. **24**:196, 1939.

Typical diabetes mellitus developed in a white boy when he was 2½ years of age. Physical examination revealed that the liver was large and firm. During the ensuing four years the size of the viscus remained unchanged; growth in length became much retarded. The hepatomegaly was thought to be due to pathologic storage of glycogen. The opinion is expressed that cases of this sort bear some poorly understood relation to von Gierke's disease. Similar cases have been described by Mauriac and by Nobécourt and his associates.

McCUNE, New York.

CONGENITAL MYXEDEMA: A FOLLOW-UP INVESTIGATION OF THE SOMATIC AND MENTAL DEVELOPMENT DURING TREATMENT WITH AN EXTRACT OF SHEEP THYROIDS. O. MARVEL, Acta pædiat. **24**:214, 1939.

Between the years 1906 and 1931 a diagnosis of congenital myxedema was made in 41 of the 5,088 children who were admitted to Rikshospitalet, Oslo. Therapeutically, whole thyroid gland was employed in doses approximating 0.3 to 0.6 Gm. (5 to 10 grains) of the fresh gland daily. In 1937 a follow-up inquiry was instituted. Of the entire group only 16 returned, 14 girls and 2 boys. The period of observation varied between six and thirty-two years. Of 12 patients over 15

years of age, only 1 had attained normal height. Anthropometric examination revealed that in general development was well proportioned. The most intelligent of the patients had an intelligence quotient of 80; the others had lower scores; 8 were idiots. No definite relationship could be found to exist between the time of commencing the treatment and the ultimate attainment of physical and mental stature. This is a copiously detailed and well documented paper.

McCUNE, New York.

HORMONE THERAPY IN DYSTROPHIA ADIPOSOGENITALIS. P. PLUM, Acta pædiat. **24**:255, 1939.

The use of gonadotrophic substances derived from the urine of pregnant women resulted in a distinct growth of the external genital apparatus in boys suffering from obesity of the so-called Frölich type. No failures were encountered. In 2 of 3 cases there occurred an increased excretion of testicular hormone in the urine.

McCUNE, New York.

## Diseases of the Muscles, Bones, Joints and Lymph Glands

ROENTGENOLOGICAL AND PATHOLOGICAL CONSIDERATIONS OF EWING'S TUMOR OF BONE. J. M. NEELY and F. T. ROGERS, Am. J. Roentgenol. **43**:204 (Feb.) 1940.

The chief difficulties in the differentiation of Ewing's tumor are presented by chronic osteomyelitis, syphilitic osteitis and metastatic neoplasm. The histologic picture may be as confusing and variable as the roentgenogram. The roentgen findings result from destructive and reparative processes in osseous tissue, any of which may be seen in osteogenic sarcoma, metastatic tumor or non-neoplastic lesions. The authors state that biopsy should never be omitted when Ewing's tumor is suspected, since there is no evidence that this procedure causes dissemination of the tumor cells.

Five cases of Ewing's tumor are presented, in which the sites of the tumor were the proximal end of the shaft of the left tibia (1 case), the fibula (2 cases) the second cuneiform bone (1 case) and the distal half of the clavicle (1 case).

SQUIRE, Chicago.

ON LIPOID GRANULOMATOSIS OF THE BONES WITHOUT SYMPTOMS OF HAND-SCHÜLLER-CHRISTIAN DISEASE. I. SNAPPER, Chinese M. J. **56**:303 (Oct.) 1939.

This disease usually attacks children. The author reports his observations on 3 patients, 2 of whom were children. In the first child the disease was initiated at the age of 7 years by fracture of a thigh; it recurred from then on until the child was 10 years of age. Small brown nevi appeared on the face and chest. Roentgenograms showed osteoporotic cystlike lesions in both femurs and comparable lesions in other bones. The absence of pain and of cranial localizations was unusual for von Recklinghausen's disease. The child died at the age of about 14 years.

The second juvenile patient was a boy of 8 years, who at 2 years had a painful and swollen condition of the right elbow, due to an involvement of the lower end of the right humerus. The lesion was shown by a roentgenogram to be a destructive one. It subsided during a period of several years, with complete return of function in the elbow. At 6½ years of age the right knee became tender and swollen, the child being in good condition except for obesity. Roentgen examination revealed an ellipsoid cystic region in the lower epiphysis of the right femur and a giant cell tumor in the lower end of the left leg, which was without pain or disability. Histologic examination of this so-called giant cell tumor showed fibrous tissue full of giant cells and numerous islands of xanthoma cells (typical

foam cells) full of doubly refractile cholesterol esters. Here, then, was another instance of lipoid granulomatosis of bone without any symptoms of Hand-Schüller-Christian disease.

The remainder of the paper is devoted to a discussion of the nature of the disease and of the reports of other observers. The writer advises that biopsies be performed on fresh lesions, because in old lesions the lipoid granuloma has been replaced by fibrous tissue, which is a terminal stage resembling osteitis fibrosa. Photographs are reproduced.

NEFF, Kansas City, Mo.

## Skin Diseases; Allergy

STUDIES ON THE SITE OF SENSITIVITY IN THE ARTHUS PHENOMENON. A. R. RICH and R. H. FOLLIS JR., Bull. Johns Hopkins Hosp. **66**:106 (Feb.) 1940.

In the Arthus type of hypersensitivity there is vascular sensitivity, but the cells of the tissues at large are not themselves sensitized. Death of tissue in the Arthus reaction results primarily from an impairment of nutrition due to vascular damage and to clogging of the tissue spaces with exudate and hemorrhage.

It has been shown by numerous investigators that if foreign protein is injected one or more times into the cornea of one eye a subsequent injection after some days leads to a more marked corneal reaction than occurs as a result of an injection of the protein into the opposite, untreated eye. This has been attributed to the development of local hypersensitivity in the treated eye. The present experiments indicate that the more marked reaction in the treated eye is due not to a higher degree of local sensitization of the corneal tissue but to the increased vascularity which results from the preliminary intracorneal injections and from which a greater amount of exudate can be derived more promptly.

AUTHORS' SUMMARY.

BACTERIOPHAGE THERAPY: I. EFFECT OF BACTERIOPHAGE ON CUTANEOUS STAPHYLOCOCCUS LESIONS IN RABBITS. II. PROPHYLACTIC AND THERAPEUTIC EFFECT OF BACTERIOPHAGE AND OF ANTIVIRUS IN EXPERIMENTAL INFECTIONS OF THE EYE. III. ON THE NATURE OF THE DELETERIOUS EFFECT OF THE LOCAL APPLICATION OF STAPHYLOCOCCUS BACTERIOPHAGE. J. BRONFENBRENNER and S. E. SULKIN, J. Infect. Dis. **65**:53, 58 and 64 (July-Aug.) 1939.

The experiments reported in these three papers are summarized as follows:

I. "Bacteriophage applied locally in the form of wet dressings, or injected intravenously is of no therapeutic value in the treatment of staphylococcus skin infection in experimentally infected animals. However, when bacteriophage and organisms are mixed just prior to intradermal injection there is a marked decrease in the size of the resultant lesion and healing progresses rapidly. On the other hand, a temporary intensification of the local reaction is produced by the immediate application of bacteriophage to the lesion."

II. "Instillations of antivirus or bacteriophage into the conjunctival sac is not sufficient to protect the cornea or the anterior chamber of the eye against a severe infection. Direct application of antivirus or bacteriophage is of no value in the treatment of eyes experimentally infected with staphylococci. Furthermore, intensification of the local reaction frequently results from the application of bacteriophage or antivirus to the lesion."

III. "The results of these experiments show that (1) a temporary intensification of the local reaction in the skin or eyes of guinea pigs and rabbits is produced by the application of bacteriophage lysates obtained with invasive strains of staphylococcus; that (2) these undesirable local reactions are due to the presence of thermostable 'Reynals spreading factor' in bacteriophage preparations obtained with highly invasive strains of staphylococcus, and that (3) bacteriophage propagated on noninvasive strains does not cause a temporary intensification of the

local reaction and, therefore, it is suggested that unfavorable reactions may be prevented by careful selection of noninvasive strains for the preparation of bacteriophage that is to be used clinically."

TOOMEY, Cleveland.

DERMATORRHEXIS (EHLERS-DANLOS SYNDROME). C. H. SMITH, J. Pediat. **14**:632 (May) 1939.

Dermatorrhexis, or rupture of the skin, occurred in a boy aged 7½ years. He showed the complete syndrome: hyperelasticity of the skin, looseness or hyperlaxity of the joints, dermatorrhexis or pronounced fragility of the skin and its blood vessels, the presence in certain locations of raisin-like molluscoid swellings and, finally, freely movable subcutaneous nodules. In such cases the molluscoid swellings are due to repeated hemorrhages into folds of skin and are found over the bony prominences; in this case, over the heels. The subcutaneous nodules are thought to represent a departure from the normal growth of fat, namely, a budlike development of freely movable lobules from the subcutaneous fat. The resulting disturbance in vascular supply may constitute a factor predisposing to necrosis of fat and its calcification. Biopsy in this case as in the others showed a thin epidermis and replacement of collagen in the corium by dense elastic tissue. The patient was treated by supportive measures, i. e., by a high caloric diet and an abundance of vitamins, iron, various preparations of liver and small amounts of aminoacetic acid. Within sixteen months the boy gained 19 pounds (8.6 Kg.) and grew 3 inches (7.5 cm.), and skin injuries were reduced to a minimum.

RAUH, Cincinnati.

VASCULAR BIRTHMARKS: DIAGNOSIS AND TREATMENT. F. YOUNG, J. Pediat. **14**:671 (May) 1939.

Hemangioma is the most common tumor of childhood. In most instances it is present at birth. It may occur in any tissue or location, but most commonly it occurs in the skin and subcutaneous tissues of the face. Pathologically and clinically there are three different types: (1) the capillary or port wine stain, (2) the hypertrophic endothelial or strawberry growth and (3) the cavernous hemangioma. Any one lesion may have characteristic areas of all three types. The therapy should be based on the type of tumor, the location and the size. With small port wine marks, gradual excision or excision and skin grafting are useful. With larger blemishes, radiation should not be used; ultraviolet irradiation may result in improvement in this type of lesion. Strawberry hemangiomas on the trunk and extremities and on the face, if small and suitably located, should be excised. If the hemangioma is large and involves facial features, surface radiation carefully controlled, electrodesiccation or the use of solid carbon dioxide is effective. The cavernous hemangioma is best treated with an injection of a sclerosing solution. If this is unsuccessful, electrocoagulation may be useful. Any large hemangioma about the face when eradicated by one of the physical agents may leave scarring which later will have to be repaired surgically.

RAUH, Cincinnati. [FROM AUTHOR'S SUMMARY.]

PINK DISEASE (ERYTHEDEMA POLYNEURITIS. INFANTILE ACRODYNIA). D. PATERSON, Practitioner **144**:404 (April) 1940.

It was pointed out by Wood (1935) that Selter, of Solingen, Germany, described this condition in 1903. Undoubtedly, up to the moment Selter's must be accepted as the first written description of the disease. It is stated by Swift, of Adelaide, Australia, that when he was house physician at the Great Ormond Street Children's Hospital, in 1885, he saw patients with pink disease there. It was not until 1914, at a conference in New Zealand, that Swift gave his first full account of the disease, based on 14 cases. The writer remembers having patients pointed

out to him by the late Dr. John Thomson of Edinburgh, in 1914, as having "Swift's disease," with raw beef hands and feet. An excellent description of the disease was given in America by Byfield (1917) and also by Emerson (1921). Wood (1921) described 100 cases. The first description in England was given by Thursfield and Paterson (1922). Postmortem observations were described later by Paterson and Greenfield (1923).

This is a clinical picture so characteristic and clearcut that once a practitioner has seen it in a child he is most unlikely ever to miss it in another. On the other hand, no word description can quite convey the full clinical picture to any one. Children with this disease are often called "teething" or "mismanaged" because there is not—until the rash comes out—anything definite to go on. The complaint is misery, anorexia, hypotonia, wasting, rapid pulse rate and often photophobia. The attitude in bed and the red hands and feet, and cheeks, complete the picture.

There is no specific treatment for pink disease. Vitamins, liver and various drugs have been suggested, but up to the moment nothing has been found particularly helpful. An all-round, well balanced diet should be maintained, together with a liberal supply of vitamins.

Recently, various writers have suggested the efficacy of vitamin $B_1$, both by the oral and by the subcutaneous route. The author has given 5 patients from 1,000 to 5,000 units of $B_1$ intramuscularly once or twice a week for three weeks, with rather mixed results. One child seemed to improve markedly and to gain weight. Three others remained exactly the same, showing no clinical improvement or reduction in the pulse rate. In a further case there was stationary weight but a definite reduction of the pulse rate from 180 to 140 per minute. The most that can be said at the time of writing is that vitamin $B_1$ is worth a clinical trial.

Parents should be prepared to take much trouble, pegging away with the general care of the child and its feeding, together with provision of artificial sunlight and, when practicable, a change of air. Complete recovery will result.

GELSTON, San Francisco.

## Miscellaneous

RELATION BETWEEN AGE AND WEIGHT AND DOSAGE OF DRUGS. W. T. DAWSON, Ann. Int. Med. **13**:1594 (March) 1940.

The various factors which influence the dosage of drugs are discussed under the headings of (1) surface area, (2) basal metabolic rate, (3) weight of the liver and (4) daily urinary volume.

READING, Galveston, Texas.

OBSERVATIONS ON THE USE OF QUINIDINE SULFATE IN CHILDREN. CHARLES R. MESSELOFF, J. Lab. & Clin. Med. **24**:574 (March) 1939.

A study of the use of quinidine sulfate for children suggests that its effects are identical with those observed in adults. Children tolerate larger doses than do adults. However, when large doses are given, frequent electrocardiograms should be taken.

MURRAY, Galveston, Texas.

PHYSICAL STRENGTH OF ADOLESCENT GIRLS. H. B. PRYOR and R. T. SMITH, J. Pediat. **14**:610 (May) 1939.

Physical strength was measured in a group of 100 girls every six months from the age of 10 to that of 17 years. Right and left hand grip scores were averaged with pushing and pulling scores and plotted against age. Strength increased with age for the total group from the age of 10 to that of 15½ years, after which the curve flattened. The girls were divided into three groups according to body build, broad (or lateral), slender (or linear) and intermediate. When curves for the strength tests in these three groups were plotted, a marked difference was

demonstrated between broad and slender girls. Broad girls were shown to possess consistently superior physical capacity when compared with slender girls through the adolescent period. Broad and slender body builds appear to represent definite and distinct endocrine patterns.

RAUH, Cincinnati. [FROM AUTHORS' SUMMARY.]

THE CASE FOR PROPHYLAXIS WITH SULPHANILAMIDE AND M. & B. 693 [SULFAPYRIDINE]. EDWARD T. HOARE, Lancet **1**:76 (Jan. 14) 1939.

Mice can be protected against infection with hemolytic streptococci by subcutaneous injection of a single dose of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) within the previous forty-eight hours. With sulfanilamide, owing to its greater solubility, a single subcutaneous prophylactic injection has little effect.

In view of animal experiments and bactericidal tests of the blood of women under treatment with sulfapyridine and sulfanilamide, the use of these drugs is suggested as a protective measure in obstetric cases (and sometimes also in operative cases) in which there is believed to be risk of infection by hemolytic streptococci.

LANGMANN, New York.

PROLONGED HYPERTHERMIA IN AN INFANT OF EIGHT MONTHS. M. LUST, Arch. de méd. d. enf. **43**:85 (March-April) 1940.

At the age of 7½ months a boy, previously in normal health, had a severe attack of rhinopharyngitis with nondiphtheritic angina and acute otitis media. Recovery was complete in fifteen days, but the baby thereafter refused all solid food, and the diet was consequently restricted to milk, cereal decoctions and fruit juices. Within four days fever was noted, reaching 39 to 40 C. (102.2 to 104 F.) and persisting for more than a month in spite of exhaustive clinical studies. Examinations of the blood and urine and roentgenologic investigations gave negative results; sulfanilamide was given without effect; the spinal fluid was normal, and the loss in weight was negligible.

Concentration of the milk by prolonged boiling (1½ liters being reduced to 1 liter) was practiced by the mother during this febrile period. When the milk was merely diluted one third with water and boiling was discontinued, the temperature fell at once to normal and remained so. Lust concludes that the aseptic hyperthermia was caused by a disequilibrium of the infant's ration.

AMESSE, Denver.

ENLARGEMENT OF THE PEDIATRIC CLINIC OF THE UNIVERSITY OF MILAN. I. NASSO, Pediatria **47**:461 (June) 1939.

Drawings and photographs describing the enlargement of the pediatric clinic of the University of Milan, Italy, are presented. Air-conditioned rooms have been provided for the care of premature infants.

MARTOCCIO, Utica, N. Y.

# Society Transactions

## THE SOCIETY FOR PEDIATRIC RESEARCH

DANIEL C. DARROW, M.D., *President*

MITCHELL I. RUBIN, M.D., *Secretary*

*Annual Meeting, Skytop, Pa., May 1-2, 1940*

### Afternoon Session

*Wednesday, May 1*

**The Antirachitic Potency of Blood Serum.** DR. JOSEF WARKANY, Cincinnati.

The normal vitamin D content of blood serum in man was calculated from the results obtained by assaying one hundred and fifty serums; six hundred line tests were performed and the results compared with those obtained with reference cod liver oil. It was found that 100 cc. of serum contains 110 U. S. P. units of vitamin D. This value seems surprisingly high if compared with figures for the vitamin D content of other mammalian tissues or body fluids.

By oral administration of vitamin D the antirachitic potency of serum can be increased considerably. Vitamin D levels in the blood a hundred times the normal are sometimes tolerated without signs of intoxication.

In vitamin D-resistant rickets the level of vitamin D in the serum can also be increased by peroral administration of vitamin D. Apparently vitamin D is absorbed without difficulty by children with this condition.

Some experiments have been performed which indicate that an intimate connection exists between the vitamin D and the proteins of the blood serum.

**Nephrocalcinosis with Chronic Tetany.** DR. D. J. MCCUNE and DR. L. G. PRAY, New York.

The patient, exhibiting Sprengel's deformity bilaterally and incomplete cleft palate at birth, was given comparatively large doses of vitamin D from early infancy until he was 2 years of age. At this time vitamin D was withdrawn, and ten days later tetany ensued. The attack yielded to familiar measures. During the next two years the child was given more than 5,000 units of vitamin D daily and medicinal calcium in an amount sufficient to bring his total daily intake to upward of 1.5 Gm. No further episodes of similar character occurred until he was 4 years of age, when these prophylactic measures were omitted.

Inquiry into the cause and pathogenesis of the tetany has yielded the following data. The serum calcium varies between 7.5 and 10 mg. and the serum inorganic phosphorus between 3 and 7 mg. per hundred cubic centimeters. The carbon dioxide–combining power of the blood has been consistently reduced to between 20 and 40 volumes per hundred and the bicarbonate to between 9 and 19 milliequivalents per liter. The serum chloride has been inconsistently elevated, occasionally reaching 115 milliequivalents per liter. The $p_H$ of the serum remains at about 7.4. There are moderate polydipsia and polyuria, with a urinary volume of between 600 and 900 cc. daily. The specific gravity of the urine varies only within the limits of 1.008 and 1.012. A trace of albumin, a moderate number of leukocytes and renal tubular epithelial cells are consistently present. The urine usually contains large amounts of amorphous calcium phosphate sediment and a varying number of casts composed of the same material. The $p_H$ of the urine shows a

strong disposition to remain fixed at about 7. The excretion of ammonia is diminished. Even during periods of tetany, when the serum calcium has fallen as low as 7.5 mg. per hundred cubic centimeters, the daily excretion of calcium in the urine remains high, varying between 40 and 100 mg. daily with an intake of less than 200 mg. per twenty-four hours. Roentgen examination has shown moderate calcification of what is inferred to be the tubular zone of the kidneys; the roentgen appearance of the skeleton was entirely normal.

Tetany occurs when the intake of calcium is reduced below 1 Gm. daily; latent tetany is activated by emotional tachypnea and by hyperventilation due to sulfanilamide. Manifestations are readily controlled by small doses of calcium chloride and larger doses of calcium lactate and also by dihydrotachysterol and by 60,000 U. S. P. units of vitamin D daily.

The following possibilities have been considered: congenital hypoparathyroidism associated with a developmental anomaly of renal function; acquired parathyroid and renal dysfunction due to overdosage of vitamin D and calcium. In addition, the hypothesis was entertained that the primary lesion was renal and of a sort that rendered the base-sparing economy inefficient. In the absence of compensatory parathyroid hyperplasia, this type of disturbance might lead to tetany by making excessive demands on the humoral depots of calcium. This hypothesis was tested by a balance study which involved successive periods of anionogen and cationogen excess. During the period of cationogen excess—as might be expected, but contrary to the hypothesis—the tetany was intensified. At present the conclusion appears inescapable that the patient suffers from some degree of hypoparathyroidism. The origin and significance of the nephrocalcinosis remain unclear. The case exhibits certain points of similarity to those reported by Butler (*J. Pediat.* **8**:489 [April] 1936) and by Albright and his associates (*Bull. Johns Hopkins Hosp.* **66**:7 [Jan.] 1940).

**Calcification of the Arteries in Infancy.** Dr. Dorothy H. Andersen and Dr. Edward R. Schlesinger, New York.

A case of renal hyperparathyroidism in infancy, with extensive calcification of the medium-sized arteries, is presented. The clinical picture was one of severe renal insufficiency with acidosis, hyperphosphatemia and hypocalcemia. The arterial calcification was first discovered in a roentgenogram of the extremities taken at 9 weeks of age; it increased progressively, causing death by infarction of a coronary artery at the age of 6 months.

At autopsy, the kidneys showed hydronephrosis, extreme fibrosis and small cysts. The parathyroids were hypertrophied, and the bones showed changes resembling osteitis fibrosa.

The case is interpreted as one of primary renal insufficiency resulting in retention of phosphate, hypocalcemia and parathyroid hyperfunction, which in turn produced osseous changes and metastatic calcification.

**Renal Excretion of Inorganic Phosphate in Relation to the Action of Vitamin D and Parathyroid Extract.** Dr. Harold E. Harrison and Helen C. Harrison, New York.

Studies were made of the physiology of renal excretion of phosphate in normal and in rachitic dogs before and after the administration of vitamin D. The renal clearances of creatinine and phosphate were determined for several successive periods after the intravenous injection of a tenth-molar solution of sodium phosphate. From these determinations it was possible to estimate the reabsorption of phosphate by the renal tubules.

The renal excretion of phosphate is one factor in the maintenance of the normal concentration of phosphate in the blood plasma. This excretion of phosphate is controlled by the extent to which the renal tubules reabsorb phosphate from the glomerular filtrate. Normally this tubular reabsorption of phosphate remains relatively constant. The administration of vitamin D increases the reabsorption

of phosphate by the renal tubules, thus producing an increase in the concentration of phosphate in the plasma. Parathyroid extract, on the other hand, decreases the reabsorption of phosphate by the renal tubules, thus decreasing the concentration of phosphate in the plasma. It seems likely that the antirachitic action of vitamin D is dependent on the demonstrated effect on the renal tubular reabsorption of phosphate.

**Treatment of Children with the Nephrotic Syndrome with Intravenously Administered Amino Acids.** Dr. Lee E. Farr, Dr. Kendall Emerson Jr. and Dr. Palmer H. Futcher, New York.

Previous studies from the Rockefeller Institute for Medical Research have shown the feasibility and safety of intravenous administration of amino acids to nephrotic children. The present study was undertaken to furnish information on the value of intravenously administered amino acids as a replacement of dietary protein in nephrotic children and to determine if large amounts of nitrogen given parenterally would materially improve the characteristic deficit of plasma protein or influence the hypoaminoacidemia.

Four children with the nephrotic syndrome were selected for study. All had been ill for more than one year and had shown no permanent diminution of nephrotic signs while fed diets optimal for the assimilation of protein. Studies of nitrogen balance were carried out for ten consecutive one week periods. During the second, fourth and sixth periods the daily ration of protein in the diet was decreased by 30 Gm. An equal decrease was made in the carbohydrate content of the diet. During the second and fourth periods 30 Gm. of casein hydrolysate and 30 Gm. of dextrose were given daily in three equal infusions. During the sixth and eighth periods the amount of casein hydrolysate was increased to 42 Gm. daily, also given in three equal portions. The quantity of intravenously administered dextrose remained at 30 Gm. The intravenously administered amino acids were tolerated, and no febrile reactions occurred. Assimilation of nitrogen remained at a constant level when intravenously administered casein hydrolysate was substituted for an equivalent amount of dietary protein. Despite positive nitrogen balances in the patients, there was no increase in the concentration of plasma protein or of plasma amino acid nitrogen. When amino acids were given intravenously in addition to the full diet, there occurred an increase in the assimilation of nitrogen which was not obtained in earlier studies in which an equivalent amount of dietary protein alone was given.

**Effect of Relative Humidity on the Insensible Loss of Weight and the Temperature of the Skin of the Newborn Infant.** Dr. John A. Anderson, Minneapolis.

By means of an accurately controlled air-conditioned chamber, it was possible to measure the rate of insensible loss of weight of unclothed newborn infants at any relative humidity. Eighty-five observations on 40 infants in whom sweating did not occur demonstrate that there is a linear decrease in the rate of insensible loss of weight with an increase in relative humidity from 17 per cent to 92 per cent. This decrease in insensible loss of weight with increasing relative humidity was associated with an increase in the temperature of the body. The increase in the temperature of the skin usually occurred first on the foot and hand and later on the abdomen and forehead. An increase in the temperature of the skin of the hand, foot, abdomen and forehead occurring at the same time, with an increase in humidity, induced a rise in body temperature as well as sweating.

These experiments on newborn infants offer evidence that to relate the insensible weight loss to energy production is probably not valid unless the portion of heat lost by vaporization is determined at various environmental relative humidities. It is possible that further studies on older infants and children may establish values which can be used for the practical prediction of the energy required for metabolism by the method of determining insensible loss of weight.

**Mechanism of the Action of Magnesium Sulfate in Reducing Hypertension in Acute Glomerulonephritis.** Dr. Mitchell I. Rubin and Dr. Milton Rapoport, Philadelphia.

During the hypertensive phase of acute glomerulonephritis an attempt was made to determine whether the lowering of the blood pressure after magnesium sulfate therapy could be correlated with a loss of water from the body. After the intravenous administration of a hypertonic solution of sucrose during the hypertensive phase, there occurred marked diuresis, with a loss of body weight, but no concomitant fall in the arterial blood pressure. In most instances after the administration of sucrose, there was actually a temporary rise in the blood pressure (because of the increased blood volume). However, when magnesium sulfate was given by intramuscular injection, the resulting fall in the blood pressure was not associated with diuresis. From these data as well as from previous studies, it is suggested that the action of magnesium sulfate is through its dilating effect on the blood vessels themselves and not through any dehydrating mechanism.

The failure of magnesium sulfate to lower the blood pressure in several instances of hypertension seemed correlated with a relatively large urinary output by these patients; therefore, the dosage employed may have been insufficient to obtain an adequate concentration of the drug in the blood.

**Primary and Whooping Cough Pneumonia in Infants.** Dr. J. S. Light, Dr. E. Walker, Dr. H. E. Zepp and Dr. H. L. Hodes, Baltimore.

A study of pneumonia in infants and young children from the bacteriologic and immunologic viewpoints is reported. One hundred and sixty-one patients with primary pneumonia were studied at the Harriet Lane Home, and 126 patients with pertussis pneumonia were studied at the Sydenham Hospital. All the patients were treated with sulfapyridine (2-[paraaminobenzenesulfamido]-pyridine) or sulfathiazole.

The most favorable site for obtaining material for culture of pneumococci was found to be the nasopharynx, and evidence is presented for the validity of representing the pneumococci isolated from such material as the cause of the pneumonia. By study of serial cultures of nasopharyngeal material at frequent intervals, it was found that the disappearance of the pneumococcus from the nasopharynx paralleled clinical improvement and that this disappearance could be used as a criterion for discontinuing drug therapy.

Type-specific agglutinins appearing in the patient's serum were studied by the microscopic hanging drop method. They were detected in 66 of 126 patients (52 per cent) with primary pneumonia, while they were found in only 13 of 52 patients (25 per cent) with pertussis pneumonia. Agglutinins are rarely present during the first three days after beginning sulfapyridine therapy, at which time clinical improvement occurs. The time of their appearance is related to the duration of the pneumonia; they appear first between the seventh and the tenth day in the great majority of cases. Apparently, recovery from pneumonia brought about by sulfapyridine is not dependent on agglutinins.

The Francis cutaneous test was carried out on a number of patients just before discharge from the hospital. About 50 per cent of them had a positive type-specific reaction. Precipitinogen corresponding to the type of pneumococcus found in the nasopharynx was demonstrated in over 75 per cent of the patients with primary pneumonia whose urine was examined three or more times.

Cross infections with various types of pneumococci were found to be surprisingly frequent in the open ward. On a number of occasions second attacks with a new type of pneumococcus were encountered. Occasionally it was possible to demonstrate agglutinins and precipitinogen in children who acquired a pneumococcus without becoming ill. These were probably instances of absorption of the antigen from the pneumococcus and the development of antibodies against it in the absence of clinical disease.

The total mortality in patients with primary pneumonia was 1 per cent and in patients with pertussis pneumonia 10 per cent. Studies of postmortem cultures of pulmonary tissue suggested that in certain cases the pneumococci had disappeared from the lung during treatment with sulfapyridine and that the patient had died of causes other than infection with pneumococci.

**Humoral Antibodies to Staphylococcus Aureus in Infants.** Dr. John A. Lichty Jr., Dr. Chris P. Katsampes and Dr. William S. Baum, Rochester, N. Y.

In a further evaluation of the significance of the anticapsular antibody to Staphylococcus aureus (described by Lyons in 1937), we have tested a possible correlation between this antibody and staphylococcus antitoxin. For this purpose, we have made titrations of antitoxin and anticapsular agglutinins to Staph. aureus on serums obtained from a group of mothers and their respective infants. Within the limits of expected variation, each baby reflected its mother's state of immunity as shown by these tests. The level of anticapsular antibody, however, varied independently of the level of antitoxin.

In view of the frequency of staphylococcic infections in infancy, these studies were extended to include quantitative determinations of the two substances in a number of these infants during the first year of life. The level of antitoxin fell strikingly during the first few months, while the agglutinin titer remained practically unchanged during the entire period of observation.

The development of a micromethod has been of great help in this study.

**Toxoplasmic Encephalitis in Children.** Dr. Albert B. Sabin, Cincinnati.

Two cases of clinically atypical encephalitis occurring in boys, 6 and 8 years of age, during October 1939 were investigated, and definite evidence of the etiologic relation of the disease to a protozoan parasite, Toxoplasma, was obtained, in 1 and suggestive evidence in the other. The outstanding features in both instances were generalized convulsions, disorientation, fever, pleocytosis without nuchal rigidity or Kernig's sign and the absence of signs pointing to involvement of the cranial nerves. One patient died thirty days after onset, and the other recovered completely on the tenth day of the disease.

The chief pathologic change, which was found in the nervous system only after searching many sections from various regions, consisted of small granulomatous foci, in whose vicinity it was occasionally possible to find morphologic forms resembling Toxoplasma. Intracerebral and intraperitoneal injection of a suspension of the fresh brain produced toxoplasmic infection in 5 of 8 mice. This strain of Toxoplasma was found to be highly pathogenic for mice, guinea pigs, rabbits, newborn chicks and rhesus monkeys and immunologically identical with the strain first isolated from a guinea pig in this country, in 1935, by Sabin and Olitsky. Injection into mice of the spinal fluid and blood obtained on the tenth day of the disease and of the blood and a suspension of the olfactory bulbs obtained post mortem yielded no Toxoplasma. Extensive studies on hundreds of laboratory mice, including the stock used in the present study, failed to reveal Toxoplasma. Neutralizing antibodies to Toxoplasma were clearly demonstrable in the human blood obtained post mortem and only questionably demonstrable in the blood obtained ten days after onset.

Spinal fluid from the second patient was injected into mice and also into 2 guinea pigs, because tuberculous meningitis was considered in the differential diagnosis. While the mice remained well, both guinea pigs died within a day of each other during the sixth week, and Toxoplasma was isolated on passage to other guinea pigs. This strain of Toxoplasma was also immunologically identical with the others but differed from them in its lower pathogenicity, for even after several passages through guinea pigs, it failed to produce disease in mice. It became

highly pathogenic for mice after several passages through mice, however, and also produced fatal infections in rabbits, chicks and the rhesus monkey. Blood obtained from this patient ten weeks after onset contained no neutralizing antibodies.

**Serum Sickness: A Preliminary Report.** Dr. Samuel Karelitz, New York; Dr. Stephen Stempion, Boston, and Dr. Aram Glorig, New York.

Children treated from one to nine days before with scarlet fever antitoxin (horse serum) were given injections of from 2 to 15 cc. of serum sickness convalescent serum (serum obtained from persons recently recovered from horse serum sickness). A reaction occurred within thirty minutes in most of these patients, manifested as an urticarial swelling at the various sites at which the therapeutic horse serum was injected, as generalized urticaria or as these reactions in addition to headache, tachycardia and general malaise. Eighty-two per cent of the patients so treated had serum sickness after the usual incubation period for serum sickness. This sickness was milder than that commonly experienced.

From an intradermal injection of horse serum, which is followed twenty-four hours later by an intravenous injection of serum sickness convalescent serum, an urticarial reaction occurred at the prepared site in the skin. When highly purified commercial diphtheria antitoxin was used to prepare the skin, this reaction was not elicited except in a much milder form. This suggests a technic for determining the potentialities for producing serum sickness of therapeutic horse serum preparations.

The ability to react to serum sickness convalescent serum can be transferred from a person treated with horse serum to one who has not been so treated.

The skin of persons treated with horse serum from one to thirty-three days before reacts to an intradermal injection of serum sickness convalescent serum with the rapid appearance of an urticarial swelling which lasts from one-half to one hour. This reaction, or cutaneous test, is less regularly positive in subjects treated with purified horse serum preparations and is negative in control subjects. It has been positive in persons sensitive to horse serum.

## Morning Session

*Thursday, May 2*

**Influence of Acute Infections on Infantile Eczema.** Dr. Albert V. Stoesser, Minneapolis.

Hansen's observations showed that the degree of unsaturation of fatty acids in the blood serum as measured by the level of iodine absorption is lower in infants with eczema than in normal controls. As a result, oils containing a high content of unsaturated fatty acids were recommended therapeutically. The babies receiving the oils were relieved in varying degrees. The inconsistent results prompted this study.

McQuarrie and Stoesser have shown that in children there is a definite lowering of the levels of plasma lipids at the height of acute infections as compared with values during convalescence. Schwartz has emphasized the fact that babies with eczema are characteristically susceptible to acute infections. In spite of the special precautions which were carried out in the hospital, in many of the eczematous babies acute infections, such as rhinitis, pharyngitis, otitis media, cervical adenitis, bronchitis and pneumonia, with high fever in some instances, eventually developed. Before, during and after these periods of infection a most accurate record was kept of the changes in the condition of the skin, and as frequently as was possible without jeopardizing the life of the patient samples of blood were drawn for analyses for lipids.

In 10 infants it was noted that the acute infections definitely reduced the levels of lipids in the plasma, especially of the unsaturated fatty acids, and that the

return to normal levels depended entirely on the rapidity and thoroughness with which the infection cleared up. During the early part of the febrile period, the eczema often improved remarkably, although no special treatment of the skin had been instituted. This period of improvement may coincide with the sudden flood of unsaturated fatty acids into the blood stream, which Boyd has claimed occurs at the onset of fever.

At the end of the febrile period, the eczema became worse and the figures for iodine absorption were low, indicating a loss of unsaturated fatty acids from the serum. Improvement followed during convalescence as soon as the levels of plasma lipids had risen to within or close to the normal range and the unsaturated fatty acids had returned to higher levels. The administration of oils of high unsaturated fatty acid content or the external application of tar hastened recovery.

These studies indicate that acute infections, especially those of the respiratory tract, play an important role in periodically disturbing the fat metabolism of the baby with eczema, and this in turn may have an unfavorable influence on the condition of the skin, regardless of the form of treatment employed. Preliminary experiments also indicate that the fever which accompanies acute infections does not in itself cause an aggravation of the cutaneous disorder of the eczematous infant.

**Relation of Excessive Intake of Carbohydrate to Diabetic Ketosis.** Dr. Waldo Nelson and Dr. I. Arthur Mirsky, Cincinnati.

Excessive intake of carbohydrate has frequently been regarded as a potent factor in the production of diabetic ketosis, the implication being that the diabetic organism cannot burn sugar and that acetone bodies arise as products of faulty oxidation of fat. Recent studies suggest that the diabetic organism can burn carbohydrate, and that acetone bodies are normal intermediary products of the oxidation of fat. Furthermore, it has been demonstrated that the production of acetone bodies is dependent solely on the ability of the liver to retain adequate amounts of glycogen for its own nutrition, acetonemia resulting only when the glycogen in the liver falls and fat is oxidized at an excessive rate in that organ.

In view of these considerations and the fact that large amounts of dextrose will stop the ketosis of the depancreatized dog receiving no insulin, the intake of carbohydrate of patients suffering from diabetes mellitus became of interest. This study reveals that the intake of as much as 800 Gm. of carbohydrate per day (total dextrose in diet, 800 Gm.) did not result in ketosis. Our observations reveal that such high carbohydrate diets may actually depress the ketonuria of diabetic subjects, even in the absence of insulin, and make it obvious that an excessive intake of carbohydrate cannot be regarded as a factor in the production of diabetic ketosis or coma.

**The Fibrinolysin Test in Rheumatic Heart Disease.** Dr. Paul L. Boisvert, New Haven, Conn.

The fibrinolysin test has been used as a laboratory aid in the Yale Pediatric clinic for four years. The test is that of Tillett and associates, who observed that the plasma clots of normal subjects are rapidly dissolved by hemolytic streptococci, while those of patients recovering from a streptococcic infection are resistant to lysis. Reaction to the test may also be positive (resistant clot) in normal newborn infants and during the early highly febrile stage of nonstreptococcic infections, notably in pneumococcic pneumonia. The frequency and persistence of positive reactions to the test in children with acute rheumatic fever have been striking, and suggest that this simple test might be a valuable clinical aid in the diagnosis of this disease. The purpose of the present study is not to attempt to throw light on the etiology of rheumatic fever but to determine whether this frequent association of positive reactions to the test with the presence of the disease will hold in a larger number of patients, in those from the dispensary as well as those from the ward, and whether the test has any prognostic value.

Fibrinolysin tests were performed at weekly intervals on 76 children with acute rheumatic fever. Sixty were ward patients and 16 were patients who were examined in the dispensary. The incidence of strongly positive reactions to the test was essentially the same for both groups, 90 per cent and 87.5 per cent respectively. Reaction to the test remained positive for a period of from two to six months.

The number of rheumatic attacks did not seem to affect the reaction to the test. The reaction was positive in 90 per cent of the 42 patients in a first attack of rheumatic fever and in the same percentage of 28 patients in a second attack. It was positive in all of 5 patients in a third attack and in the 1 patient in a fourth attack.

There was some evidence that the presence of active carditis might influence the results of the test. Of 42 patients in a first attack of rheumatic fever, 25 of the 26 patients with well defined heart disease had positive reactions, while results were positive in only 6 of 9 patients in whom there was no evidence of heart disease, and all of the 7 patients who died while the cardiac infection was active had positive reactions to the test.

No prognostic value can be attached to the test at this time. The observations do suggest that the test may be of aid in the diagnosis of acute rheumatic fever. It is known that it is not specific for this disease, but in practice—when it is used in patients suspected of having rheumatic fever—it has been found reliable.

**Studies on an Epidemic of Scarlet Fever in Romania, N. Y.** Dr. Francis F. Schwentker and Dr. John H. Janney, New York.

Preceding and during an epidemic of scarlet fever in a village previously free of the disease, there occurred a slight rise in the number of normal carriers of hemolytic streptococci and a marked rise in the number of carriers harboring organisms of group A. Type 10 streptococcus had not been found in the village before the epidemic but was introduced in some unknown way, since it was isolated from all patients with streptococcic tonsillitis and from many normal carriers after the onset of the epidemic.

**Some Properties of the Virus of Influenza.** Leslie A. Chambers and Werner Henle, Philadelphia.

Filtered suspensions of finely ground lungs from mice infected with the W S strain of Haemophilus influenzae yielded a highly infectious sediment on repeated centrifugation at high speed (25,000 revolutions per minute for twenty minutes). The collected material, in bulk, was gelatinous, translucent and reddish brown. When resuspended in physiologic solution of sodium chloride, all the preparations contained 100 per cent of the infectivity of the original raw filtrate, and in a few instances the mouse titrations showed from a hundredfold to a thousandfold increase in infectivity, the cause of which is not yet known.

The resuspended particles were precipitated at $p_H$ 5.3 or less, while at $p_H$ 10 partial solution occurred. Dark field examination showed bodies of fairly uniform size, low refractivity and no marked asymmetry. The particles did not stain typically with the usual nuclear and acidophilic dyes but were blackened by osmic acid and stained readily with acid fuchsin or with Janus green B, which suggests a possible mitochondrial origin.

Calculations based on Elford's ultrafiltration data indicate a "molecular weight" of about $4.08 \times 10^8$ for the virus. The centrifugal force used in our experiments was of such order that no large proportion of particles of molecular weight of less than $4.0 \times 10^7$ could have been present in the sediments. Some of the preparations were infectious in dilutions up to $10^{-11}$ in doses of 0.05 cc. Thus the minimal infectious dose was $3.4 \times 10^{-15}$ Gm., or more than 5 particles. An effort is being made to determine whether the particles are the virus itself or serve as carriers for considerably smaller infectious units.

Suspensions of ground normal mouse lungs also yielded sediments of particles indistinguishable, except for infectivity, from those separated from diseased tissue. The two preparations were identical in solubility and in morphologic, optical and staining properties. Furthermore, the limited analytic data available indicate a striking similarity in chemical composition. The yield (dry weight) per lung was about 0.5 to 0.6 mg. in each case. The percentages of nitrogen, phosphorus and ash were 7.8 to 8.5, 1.21 to 1.22 and 6.1 to 7.7 respectively. Both preparations gave a strongly positive reaction to the Molisch test, a positive reaction to the Bial test and a negative diphenylamine reaction. Therefore, it is suggested tentatively that ribose nucleoprotein makes up at least part of the material.

Because of the marked similarities between the infectious and noninfectious particles, it seems advisable to investigate the possible relation between some normal cell component (mitochondria?) and the infectious process.

**Clearance of Bilirubin from the Blood.** Dr. A. A. Weech, New York.

The rate of removal from the circulation of intravenously injected bilirubin can be evaluated as a "velocity constant of excretion," which provides an accurate measure of the excretory function of the liver. The measure is not affected, as is the older type of clearance test, by elevation of the basal bilirubin concentration of the plasma.

Evaluation of the velocity constant is based on the assumption that circulation of a normal amount of bilirubin depends on an equilibrium between the rates of formation and excretion and on the observation that the rate of excretion at any time is closely proportional to the square of the concentration in the plasma. The velocity constant has been computed in units which express the rate of excretion from each 100 cc. of plasma in milligrams per minute per milligram squared in the circulating plasma. In children with presumably normal livers the constant has varied from $3 \times 10^{-3}$ to $9 \times 10^{-3}$ mg. per minute; in 3 children with hepatic disease (cirrhosis) the constants were $1.1 \times 10^{-3}$, $1.4 \times 10^{-3}$ and $1.5 \times 10^{-3}$ mg. per minute.

Calculation of the velocity constant requires three determinations of the concentration of bilirubin in the serum. The level before injecting bilirubin, $L_{eq.}$, is measured first. The injection, 5 mg. per kilogram of body weight, is then given. After a lapse of five to seven minutes to allow for mixing in the circulation, a second sample, $L_1$, is obtained. Finally, when from two to four hours has elapsed, the third sample, $L_2$, is withdrawn. If $t_1$ and $t_2$ represent the time in minutes corresponding to the samples $L_1$ and $L_2$ which express concentration in milligrams per hundred cubic centimeters of serum, the value of the velocity constant, K, can be computed from the equation:

$$K = \frac{1.1513}{L_{eq.}(t_2 - t_1)} \quad \log. \frac{(L_2 + L_{eq.})}{(L_2 - L_{eq.})} \frac{(L_1 - L_{eq.})}{(L_1 + L_{eq.})}$$

**Study of Iodine Metabolism in Hypothyroidism by the Use of Radioactive Iodine.** Dr. William A. Reilly, Dr. Joseph Hamilton and Dr. Mayo Soley, San Francisco.

It has been accepted that hypothyroidism and myxedema are caused by insufficient thyroid function or athyreosis. Until radioactive isotopes of iodine were discovered, there was no method of studying iodine metabolism of the thyroid in the intact animal. We have recently studied 4 children with severe hypothyroidism or myxedema by giving them orally 14 mg. of sodium iodide containing a known amount of radioactive iodine isotope ($I^{131}$)and then quantitating the uptake of iodine into the thyroid gland by a Geiger-Muller counter. In all patients the thyroid took up less than one-tenth as much iodine as did the thyroids of normal subjects.

Fibrinolysin tests were performed at weekly intervals on 76 children with acute rheumatic fever. Sixty were ward patients and 16 were patients who were examined in the dispensary. The incidence of strongly positive reactions to the test was essentially the same for both groups, 90 per cent and 87.5 per cent respectively. Reaction to the test remained positive for a period of from two to six months.

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Preceding and during an epidemic of scarlet fever in a village previously free of the disease, there occurred a slight rise in the number of normal carriers of hemolytic streptococci and a marked rise in the number of carriers harboring organisms of group A. Type 10 streptococcus had not been found in the village before the epidemic but was introduced in some unknown way, since it was isolated from all patients with streptococcic tonsillitis and from many normal carriers after the onset of the epidemic.

**Some Properties of the Virus of Influenza.** Leslie A. Chambers and Werner Henle, Philadelphia.

Filtered suspensions of finely ground lungs from mice infected with the W S strain of Haemophilus influenzae yielded a highly infectious sediment on repeated centrifugation at high speed (25,000 revolutions per minute for twenty minutes). The collected material, in bulk, was gelatinous, translucent and reddish brown. When resuspended in physiologic solution of sodium chloride, all the preparations contained 100 per cent of the infectivity of the original raw filtrate, and in a few instances the mouse titrations showed from a hundredfold to a thousandfold increase in infectivity, the cause of which is not yet known.

The resuspended particles were precipitated at $p_H$ 5.3 or less, while at $p_H$ 10 partial solution occurred. Dark field examination showed bodies of fairly uniform size, low refractivity and no marked asymmetry. The particles did not stain typically with the usual nuclear and acidophilic dyes but were blackened by osmic acid and stained readily with acid fuchsin or with Janus green B, which suggests a possible mitochondrial origin.

Calculations based on Elford's ultrafiltration data indicate a "molecular weight" of about $4.08 \times 10^8$ for the virus. The centrifugal force used in our experiments was of such order that no large proportion of particles of molecular weight of less than $4.0 \times 10^7$ could have been present in the sediments. Some of the preparations were infectious in dilutions up to $10^{-11}$ in doses of 0.05 cc. Thus the minimal infectious dose was $3.4 \times 10^{-15}$ Gm., or more than 5 particles. An effort is being made to determine whether the particles are the virus itself or serve as carriers for considerably smaller infectious units.

Suspensions of ground normal mouse lungs also yielded sediments of particles indistinguishable, except for infectivity, from those separated from diseased tissue. The two preparations were identical in solubility and in morphologic, optical and staining properties. Furthermore, the limited analytic data available indicate a striking similarity in chemical composition. The yield (dry weight) per lung was about 0.5 to 0.6 mg. in each case. The percentages of nitrogen, phosphorus and ash were 7.8 to 8.5, 1.21 to 1.22 and 6.1 to 7.7 respectively. Both preparations gave a strongly positive reaction to the Molisch test, a positive reaction to the Bial test and a negative diphenylamine reaction. Therefore, it is suggested tentatively that ribose nucleoprotein makes up at least part of the material.

Because of the marked similarities between the infectious and noninfectious particles, it seems advisable to investigate the possible relation between some normal cell component (mitochondria?) and the infectious process.

**Clearance of Bilirubin from the Blood.** DR. A. A. WEECH, New York.

The rate of removal from the circulation of intravenously injected bilirubin can be evaluated as a "velocity constant of excretion," which provides an accurate measure of the excretory function of the liver. The measure is not affected, as is the older type of clearance test, by elevation of the basal bilirubin concentration of the plasma.

Evaluation of the velocity constant is based on the assumption that circulation of a normal amount of bilirubin depends on an equilibrium between the rates of formation and excretion and on the observation that the rate of excretion at any time is closely proportional to the square of the concentration in the plasma. The velocity constant has been computed in units which express the rate of excretion from each 100 cc. of plasma in milligrams per minute per milligram squared in the circulating plasma. In children with presumably normal livers the constant has varied from $3 \times 10^{-3}$ to $9 \times 10^{-3}$ mg. per minute; in 3 children with hepatic disease (cirrhosis) the constants were $1.1 \times 10^{-3}$, $1.4 \times 10^{-3}$ and $1.5 \times 10^{-3}$ mg. per minute.

Calculation of the velocity constant requires three determinations of the concentration of bilirubin in the serum. The level before injecting bilirubin, $L_{eq.}$, is measured first. The injection, 5 mg. per kilogram of body weight, is then given. After a lapse of five to seven minutes to allow for mixing in the circulation, a second sample, $L_1$, is obtained. Finally, when from two to four hours has elapsed, the third sample, $L_2$, is withdrawn. If $t_1$ and $t_2$ represent the time in minutes corresponding to the samples $L_1$ and $L_2$ which express concentration in milligrams per hundred cubic centimeters of serum, the value of the velocity constant, K, can be computed from the equation:

$$K = \frac{1.1513}{L_{eq.}(t_2 - t_1)} \log. \frac{(L_2 + L_{eq.})}{(L_2 - L_{eq.})} \frac{(L_1 - L_{eq.})}{(L_1 + L_{eq.})}$$

**Study of Iodine Metabolism in Hypothyroidism by the Use of Radioactive Iodine.** DR. WILLIAM A. REILLY, DR. JOSEPH HAMILTON and DR. MAYO SOLEY, San Francisco.

It has been accepted that hypothyroidism and myxedema are caused by insufficient thyroid function or athyreosis. Until radioactive isotopes of iodine were discovered, there was no method of studying iodine metabolism of the thyroid in the intact animal. We have recently studied 4 children with severe hypothyroidism or myxedema by giving them orally 14 mg. of sodium iodide containing a known amount of radioactive iodine isotope ($I^{131}$)and then quantitating the uptake of iodine into the thyroid gland by a Geiger-Muller counter. In all patients the thyroid took up less than one-tenth as much iodine as did the thyroids of normal subjects.

While the group is small, the work suggests that one reason for the hypothyroidism in such patients is the inability of the thyroid to utilize iodine for the synthesis of a metabolically active hormone.

This work is part of a comprehensive study using a new approach to the problem of iodine metabolism and the physiology of the thyroid.

**Results of Surgical and Medical Treatment of Exophthalmic Goiter of Children.** Dr. Roger L. J. Kennedy, Rochester, Minn.

A follow-up study was made of 171 patients who had received treatment for exophthalmic goiter in childhood. Late information was received concerning 163 of the 171 patients.

The ratio by sex was 7.5 females to 1 male. The ages of the patients at the time that treatment was begun ranged from 3 to 14 years. Reports were received from patients who had been first seen as long as thirty-one years previously.

The immediate results of surgical treatment were good or fair in most cases, but the results of treatment were much improved after iodine came into use in 1922. Five of 55 patients operated on before iodine came into use died in the hospital. Hence the mortality rate in that group was 9 per cent. Three of the 91 patients operated on after iodine came into use died in the hospital. Hence the mortality rate in that group was 3 per cent.

The late results in 105 or 138 cases in which treatment was surgical were entirely satisfactory. In 23 instances results were fair, and in 2 instances they were poor. Recurrences were either mild or severe and occurred in 12 cases. Subsequent operations were done in 17 cases. Most of these operations were carried out on patients originally treated before the advent of iodine medication.

Low metabolic rates and postoperative myxedema were more frequent among the group of patients treated by extensive resection. These were easily controlled by administration of desiccated thyroid gland.

In 13 cases in which treatment was surgical, other pathologic conditions of major importance were present, either at the time of operation or subsequently.

Twenty-five patients were treated medically. Seven of the 25 were operated on elsewhere at a later date. Of the patients who died, 3 were in critical condition at the time of arrival. In a few cases of mild involvement the disease appears to have been controlled by medical treatment, which consisted of restriction of activities and administration of iodine.

Children with exophthalmic goiter apparently grow more rapidly than so-called normal children, but the heights ultimately attained by these children are not greater than the average.

**Relation Between Fetal Position and Certain Congenital Deformities.** Dr. Charles C. Chapple, Philadelphia.

An attempt was made to determine the role of fetal position in the genesis of certain congenital deformities by folding each newborn infant into the position which was obviously the most comfortable one for that infant. Capsular relaxation was discovered to exist for a period varying from five days to one month after birth. During this pliant period the "position of comfort" might include a posterior dislocation of the knee, for example, which would disappear as the relaxation disappeared provided the angle had been slight but would persist as a back knee if the angle had been greater. This capsular relaxation occurs in varying degrees and may be due to the relaxing hormone of the mother. One infant was again relaxed when she lost her pliancy by the administration of estrogen.

In the presence of great relaxation there can be no pressure of the femoral head into the acetabulum in the fetal position. Absence of pressure delays the ossification of the epiphysial centers of either or both bones and results in congenital dislocation of the hip.

Deviations of the jaw, torticollis, dislocations of the shoulder, elbow, wrist and fingers, as well as both anterior and posterior dislocation of the knee and clubfoot are included in the series. In each case, the "position of comfort" explained the deformity on a basis of relaxation and uterine pressure. Determination of the "position of comfort" led to the diagnosis of deformities which were otherwise unsuspected.

**Vitamin K and Hemorrhagic Disease of the Newborn.** Dr. C. E. Snelling, Toronto, Canada.

Natural vitamin K may be given by mouth, and the synthetic vitamin may be given intravenously as well, with no ill effects, to persons of all ages.

The prothrombin clotting time of the cord blood is prolonged in a large number of newborn infants, at times without any clinical bleeding.

Daily administration of synthetic vitamin K by mouth to mothers for from two to sixteen days before delivery had no effect on the prothrombin clotting time of their blood but resulted in a shorter prothrombin clotting time of the cord blood. This administration is recommended as a preventive measure against hemorrhagic disease.

The prothrombin clotting time in hemorrhagic disease of the newborn is prolonged, and with the arrest of bleeding it is materially shortened. Vitamin K given by mouth may not be retained or absorbed, and so it is not safe to depend on the orally administered vitamin as the sole means of treatment.

Intravenous administration of synthetic vitamin K will lower the prothrombin clotting time and arrest bleeding in hemorrhagic disease of the newborn. If the hemoglobin content is low, transfusion should be used in addition.

**Preliminary Studies on the Determination of Alpha and Beta 17-Ketosteroids (Androgens) in Urine.** Dr. Nathan Talbot, Brookline, Mass., E. E. MacLachlan and Dr. Allan M. Butler, Boston.

**Studies on Vitamin $B_1$ Metabolism.** Victor A. Najjar, Baltimore.

By the use of the thiochrome procedure described by Hennessey and Cerecedo, determinations of the concentration of thiamine have been carried out on the urine of normal and pathologic subjects of various ages. Values for standards are given.

Since it is not possible to correlate closely clinical deficiency with the daily excretion of thiamine several excretion tests have been studied in order to throw light on the state of thiamine stored in the body. The most satisfactory procedure tried has been a four hour urinary excretion test following an intravenous dose of 1 mg. of thiamine. The results of such tests have been shown in normal adults, in children and in subjects with various pathologic conditions, including deficiency states, diabetes and diarrheal disorders.

By a modification of the thiochrome procedure, it has been possible to determine the concentration of thiamine in the blood. Observations on the thiamine disappearance curve following an intravenously administered dose of thiamine are presented.

# Book Reviews

**"Breathing Machines" and Their Use in Treatment.** The Respirators (Poliomyelitis) Committee. Price, 2s. net. Pp. 90, with 15 illustrations. London: His Majesty's Stationery Office, 1939.

So much has been written about breathing machines that it would be worth while for every one to read the report of this committee. It is authoritative and lacks the bias and hysteria that characterize so many pseudoscientific articles on the subject.

The committee first tried to determine the approximate number and types of patients in England and Wales who required the aid of breathing machines. It would seem that such statistics should also be available and easily obtained in the United States. Those who work in this field have had the impression that there are perhaps not so many patients who need respirators as is thought. That impression is confirmed by this report. Although the committee found that patients with poliomyelitis were in the majority, the group included persons with many other clinical disorders, such as postdiphtheritic paralysis, respiratory paralysis following administration of narcotics, acute toxic polyneuritis, progressive muscular atrophy, spontaneous hematomyelia, spinal tumor, intracranial hemorrhage, tumor or abscess, meningitis, neuromyelitis optica, postvaccinal encephalomyelitis, myasthenia gravis, botulism, tetanus, disseminated myelitis, injury of the spine, postoperative respiratory failure and drowning.

The conclusions of the committee are: 1. The principal causes of asphyxia are drowning and gas poisoning, for which breathing machines are not required; manual artificial respiration and oxygen are all that is necessary. 2. A machine neither takes the place of nor compares in usefulness with the training of all members of a community in the manual methods of artificial respiration. Manual methods must never be postponed in an emergency because of the mistaken idea that a patient can be better treated with a machine. 3. Breathing machines are required only for protracted failure of respiration.

Practically all the machines now used are modifications of Woillez' spirophore, described in 1854 and 1875. The most common are the Drinker respirator, the Drinker-Collins respirator, the Emerson respirator, the Henderson respirator, the Siebe Gorman "Drinker" respirator, the Both respirator, the barospirator, the biomotor, the Sahlin, or Stille, respirator, the Bragg-Paul pulsator, the Burstall jacket respirator, the London County Council cuirass respirator, the Turner jacket respirator, the Laffer Lewis apparatus, the Eve motor rocking bed, the Panis resuscitator, tilting stretchers, Héderer's pulmoventilator, Cot's apparatus, the McKesson resuscitator, the Oxford inflator and the Boulette inflator.

Many of these machines have specialized uses; the choice of machine depends on the length of time the patient is going to need the respirator and whether he is to get positive or negative pressure. If the emergency is brief in point of time, insufflators of the McKesson design, with positive oxygen pressure, or tilting machines, made according to Eve's principle and operated either by motor or by hand, are perhaps the most suitable.

There are two types of respirators for prolonged use. They are (1) cabinets in which all of the body but the head is enclosed and (2) machines which enclose only part of the body. Of the cabinet type, the Drinker and Both respirators are believed to be efficient. The Bragg-Paul pulsator, which exerts positive pressure on the chest, is thought to have an advantage over the machines which enclose only part of the body in that it is simple in design and allows free access to the patient. It is stated, however, that this respirator has not been established as efficient in all forms of respiratory failure. The authors frankly conclude that negative pressure cuirasses, although interesting, are in the experimental stage.

They express the belief that there is no need to scatter respirators all over England. They advise centralization on the grounds that the patient who needs a respirator usually requires especially skilled treatment, which the average physician lacks. They also express the opinion that it is easy enough to transport a patient with respiratory failure for a considerable distance and that it should be the rule to move the patient to the machine and not the machine to the patient.

The authors discuss the indications for the use of breathing machines and the management and technic of nursing the patient while in the machine. The report considers all machines in detail, and includes references to published experiences with each type and illustrations. There is a complete bibliography.

**Die einheimische Sprue.** By Heinrich Hotz. Price, 3.80 marks. Pp. 44, with 6 illustrations. Stuttgart: Ferdinand Enke, 1940.

In this excellent monograph Hotz first gives a brief historical review of endemic nontropical sprue and then lists the cardinal symptoms. Usually the onset of diarrhea is sudden, and it persists for weeks or months, in spite of treatment. The abdomen becomes markedly distended; buccal aphthous ulcers often appear; the tongue burns; emaciation becomes extreme—a loss of weight of 10 Kg. may occur within several weeks or months. Diagnosis is possible from the foregoing clinical picture if the disease has progressed sufficiently. Steatorrhea occurs in all cases (fat is seen microscopically in the stools, more frequently as fatty acid crystals; stools have an acid reaction; the skin gradually assumes a gray-brown coloration) often with an icteric tinge not like that of pernicious anemia but more like that of Addison's disease. Hypocalcemia (concentrations below 9 mg. of calcium per hundred cubic centimeters) and hypophosphatemia occur and may lead to tetany. Megaloblasts are found in the bone marrow and megalocytes in the blood of patients with nontropical sprue.

Nontropical sprue is not caused by a single factor. A disturbance in the absorption of fat leads promptly to a vitamin deficiency. Endocrine disturbances are probably secondary to insufficient vitamin absorption, for example, an adrenal cortical insufficiency may be due to lack of absorption of vitamins C and $B_2$. Nontropical sprue differs from Herter's infantilism (celiac disease) in that it does not interfere with growth.

Fanconi's diet for celiac disease, of raw fruits (ripe banana, grapefruit, berries) and vegetables (carrot and tomato juices, asparagus purée), is beneficial in the treatment of nontropical sprue. Hotz found protein milk and lean meat (preferably beef and fish) very important; he also used eggs. Grated cheese, yoghurt, zwieback and barley flour were added for increasing weight. Five meals were fed daily. The anemia responded to liver and iron therapy.

**As the Twig is Bent.** By Leslie B. Hohman, M.D. Price, $2.50. Pp. 291, with no illustrations. New York: The Macmillan Company, 1940.

"Spank if you must."

"A high-tempered, strong and obstinate child can be immobilized quickly, its arms and legs pinioned, without the least danger of injury and with a minimum of anger-arousing conflict." This treatment was prescribed for a 12 year old girl. The author reports that it was successful.

". . . but the teacher insisted kindly that the baby finish each course and finish the entire meal before she could play."

"For the correction of detrimental moods, furniture-breaking youngsters should be wrapped and pinned in several layers of blankets and left severely alone until their excitement passes—this remedy is recommended for extreme cases of gloominess that have gone beyond other controls."

For the treatment of an attractive 2½ year old girl with an excellent health record who, for unknown reasons, began screaming and would not stay in bed for the first time in her life: "the girl was rolled and pinned tightly in blankets from chin to toes. She screamed for 50 minutes as measured by the clock."

Such ideas as those reflected in these quotations from various parts of the book give the reviewer the impression that it is reactionary; it ignores the great improvement in child-rearing technics and the increased knowledge of mental growth which have been described during the past twenty years. In fairness to the book, however, it should be emphasized that, aside from the methods advocated for disciplining children, it contains much valuable information.

Chapters are devoted to "Illness—Real and Otherwise," "Ultra-Modern Education," "Movies," "Radio," "Will They Outgrow It?" "Day Dreams and Fairy Tales," "Sex Education" and "Adolescence," to mention a few of the more instructive ones.

The book has a clear, concise form and an interesting style.

**Physical Therapy for Nurses.** By Richard Kovacs, M.D. Second edition. Price, $3.25. Pp. 335, with 99 illustrations and 27 tables. Philadelphia: Lea and Febiger, 1940.

Realizing that physical therapy is one of the rapidly growing allies of medicine, Dr. Kovacs has reedited his book "Physical Therapy for Nurses," bringing up to date the various phases of physical therapy technic.

The book deals with the essentials of physics, chemistry and biophysics and offers instruction in the application of heat, electricity, light, water, massage and exercise.

Dr. Kovacs has the happy faculty of presenting technical knowledge in an entertaining and easy style, which should make his book an excellent reference for the physician and his office assistant, if he has any of the modern physical therapy equipment and has not the services of a trained physical therapeutist at his disposal.

The chapters on fever therapy, short wave diathermy and colonic irrigation are new, and those on heliotherapy, the use of artificial light, electrotherapy and hydrotherapy have been revised to include the most recent theories and methods.

This volume is an excellent adjunct to, but not a substitute for, supervised instruction in physical therapy, as it would be impossible to include in a manual all varieties of treatment which are required in the ordinary physical therapy department. This is especially true in regard to the portion of the book devoted to the work in which the technician spends the greater portion of her active treatment of the patient—massage and exercise—as it is virtually impossible to learn these two forms of treatment without prolonged and careful instruction and supervision.

**Illustrative Electrocardiography.** By Dr. Julius Burstein. Second edition. Price, $5.00. Pp. 292, with 106 illustrations. New York: D. Appleton-Century Company, 1940.

The title of this book describes it very well. It consists almost entirely of reproductions of electrocardiograms which illustrate both normal findings and abnormal deviations. Accompanying each illustration is a brief but clearcut description of the significant points demonstrated. The material is well arranged and comprehensive. The arrhythmias are dealt with in detail. The section dealing with coronary occlusions is not quite so complete. However, the classic types are adequately illustrated. Especially helpful are the serial curves from several cases of coronary occlusion. These demonstrate well the electrocardiographic deviations at the time of the occlusion and the changes in the days and weeks following. In several instances serial curves are shown which extend over a period of years following the occlusion.

The section on precordial leads is excellent and includes the report of the Committee for the Standardization of Precordial Leads. This report, together with the illustrations, should help to clarify some of the confusion which has existed in regard to precordial leads. The illustrations showing the types of heart block are well selected. Electrocardiographic changes due to digitalis are also clearly shown.

It is to be regretted that the book does not give more attention to the variations seen in electrocardiograms of infants and children and that it deals all too briefly with congenital heart disease.

**Newer Nutrition in Pediatric Practice.** By I. Newton Kugelmass, M.D. Price, $10.00. Pp. 1,155, with 183 illustrations, 422 tables. Philadelphia: J. B. Lippincott Company, 1940.

The author states in the preface to this book that its purpose is "to incorporate proved nutritional knowledge into the entire field of clinical pediatrics for the dual purpose of buoyant positive health and effective nutritional therapy."

The first part deals with nutritional physiology and contains data on maintenance, the metabolism of food stuffs, the vitamins and salts and digestion and absorption. The second section is concerned with the nutrition and the food requirements of the newborn baby, the infant and the child. The final section takes up nutrition in various diseases, including digestive, deficiency, metabolic, allergic and infectious disorders and regional diseases.

Such a bare outline of the salient topics does not by any means give the full scope of this book. An immense amount of work must have been necessary to write this book. Subjects are discussed in the most complete detail, and it is surprisingly up-to-date, a seeming impossibility in such a broad field. The many detailed tables, charts and diets cover the whole field of pediatrics.

The author seems to have accomplished his purpose so admirably that this book might well become a standard for this type of work. There is an excellent bibliography at the end of each chapter, which adds to its value as an excellent book for reference.

**Growth and Development of the Young Child.** By Winifred Rand, A.B., R.N.; Mary E. Sweeny, M.S., M.A., and E. Lee Vincent, Ph.D. Price, cloth, $2.75. Pp. 462, with 55 illustrations and 36 tables. Philadelphia: W. B. Saunders Company, 1940.

The director of parent education, Winifred Rand, the nutritionist, Mary Sweeny, and the psychologist, E. Lee Vincent, of the Merrill-Palmer School, Detroit, have worked together in the production of this unusual study of the growth and development of the young child. The content of the book truly lives up to the title, for here are shown not only what the child should do at various ages but how he grows in ability, what hinders him and what helps him to the fullest extent. One is made to see what factors enter into his physical growth and dexterity but especially his intellectual growth and the development of his social accomplishments. Social accomplishment does not mean the acquiring of superficial social graces but a real ability to live with others as a happy and useful citizen.

The first part has to do with development during infancy, and the later sections deals with the later period of early childhood. Although there is no pretense of covering the field of adolescence and adult life, much that is said is applicable to these periods. The chapters on family relationship are particularly interesting.

This book should be of great value to parent, teacher and physician and, in fact, to any one interested in the development of adult standards of behavior.

**Care of Poliomyelitis.** By Jessie L. Stevenson, R.N. Price, $2.50. Pp. 230, with 43 illustrations. New York: The Macmillan Company, 1940.

If one reads "between the lines," the epic fight made by the Chicago Visiting Nurses Association against infantile paralysis is incorporated in this valuable book by Jessie L. Stevenson.

The author was in charge of the Visiting Nurses Association's service for poliomyelitis for a number of years, and because of her intensely practical experience a printed record of her knowledge is valuable. Problems are clearly pre-

sented from the nursing standpoint and include discussions of the various phases of convalescent care in infantile paralysis. Illustrations are provided wherever the text needs amplification and in particular to demonstrate many features peculiar to poliomyelitis.

Perhaps no part of the book is so valuable as the appendix which describes the making of splints. The exquisitely simple but ingenious splints which are shown have been proved efficient again and again. The general practitioner of medicine could find excellent use for these temporary splints. No general hospital with wards for the care of infantile paralysis should fail to have a copy of this book on the head nurses' desk for reference.

Miss Stevenson has written her book in a simple, readable style, and as a practical work on the care of patients with infantile paralysis it has no equal.

**Panum on Measles.** By Peter Ludwig Panum, M.D. (translated from the Danish by Ada Sommerville Hatcher), with a biographical memoir by Julius Jacob Petersen, M.D. (translated from the Danish by Joseph Dimont), and an introduction by James Angus Doull, M.D. Price, $2.50. Pp. 111, with 1 illustration. New York: The American Public Health Association, 1940. Published by the Delta Omega Society.

This translation of the original report of Panum on an epidemic of measles in the Faroe Islands is accompanied by an introductory chapter and a biography. It is followed by appendixes containing supplementary reports.

To the reader this report of an epidemic disease in an isolated group of islands almost a hundred years ago is most interesting, not only from an epidemiologic but from a historical standpoint. While the reviewer confesses no familiarity with conditions in the Faroe Islands at that time, he is struck with the detailed description of the life in these islands, which is of great medical interest and must also be of great general interest. If one reads this description of the measles epidemic there, at the same time trying to realize the medical background of a physician of a hundred years ago, one may well be astounded by the accuracy and keenness of the observations.

The book is well worth reading.

**Principles of Orthopedic Surgery.** By James Warren Sever, M.D. Third edition. Price, $3.25. Pp. 418, with 221 illustrations. New York: The Macmillan Company, 1940.

The subject matter of this book truthfully lives up to its title. It furnishes a small, but very practical, text for students and in particular for nurses.

The book is not in any sense of the word a reference work, although illustrations and material provide a source of information for those students who otherwise might not see the complete range of orthopedic conditions.

Controversial subjects have been avoided, and there are omissions of minor importance of discussion in the less well known conditions.

The author approaches study and treatment from his own personal viewpoint, and because of his wide experience the discussion is sound, even though didactic. Some of the arrangement of subject matter is unusual and departs from the generally accepted orthopedic classifications. A chapter has been included on the social condition of the crippled child, an aspect that very definitely affects his medical care, and in another chapter there is an excellent discussion of braces and appliances.

Because of its practical nature, Sever's book has long been recommended for nurses, and this edition exceeds the previous ones in value.

**L'enfant et l'adolescent instables.** By Jadwiga Abramson. Price, 40 francs. Paris: Presses Universitaires de France, 1940.

The first part of this book is devoted to a detailed review of the literature on the unstable child and adolescent. The second portion gives 87 case reports, grouped according to the author's interpretation as to whether they represent

primary instability or instability associated with definite motor disturbances, with perversion, with epilepsy or with paranoia.

The last part of the book is concerned with a study and analysis of the intellectual, motor and emotional status of the patients in the various groups. In general it appears that the intellectual abilities were hampered by lack of perseverance and judgment, the motor ability showed lack of precision and the affective life showed persistence of such infantile traits as outbursts of undirected energy and temper, failure to subordinate immediate satisfactions to a larger good and rebellion against any authority.

The scope of this work does not include a study of the causes of instability. The author, however, seems to consider constitutional or hereditary factors as playing the greatest role.

There is no table of contents or index. This is a decided lack in so detailed and long a book.

**The First Five Years of Life: A Guide to the Study of the Pre-School Child.** By Arnold Gesell and others. Price, $3.50. Pp. 393, with 21 plates, many illustrations and tables. New York: Harper and Brothers, 1940.

This book presents a comprehensive, objective clinical picture of the mental and physical developmental patterns of the first five years. It is almost entirely descriptive, portraying the behavior of normally developing children, with no attempt to theorize regarding behavior patterns.

This authoritative work from the Yale Clinic probably gives the most accurate picture of physical and intellectual growth which has appeared. Motor development, adaptive behavior, language development and personal-social behavior are described separately for the successive levels from four weeks to five years.

Like all of the books by Gesell and his associates, this book is written in a very direct style, the terminology is easily understood and it is interesting throughout. It should be read by every one working with children.

**Psychiatric Clinics for Children.** By Helen Leland Witmer, Ph.D. Price, $2.50. Pp. 437, with 6 tables. New York: The Commonwealth Fund, 1940.

This well written and interesting volume describes the theory, practice and procedures and gives an evaluation of child psychiatric clinics in this country. The book not only takes up the problems of clinics but includes chapters on feeblemindedness and the prevention of delinquency.

The book is an objective, apparently unbiased description of mental hygiene clinics for children in this country. The author has obviously devoted a great deal of time and thought to the subject. The material is well organized and of value to those who are interested in child guidance.

**The Compleat Pediatrician.** By W. C. Davison, M.D. Price, $3.75. Pp. 312. Durham, N. C.: Duke University Press, 1940.

In the third edition of this very interesting and practical book the author has chiefly polished some of the rough edges and brought the context more completely up to date. He states that information was taken from 3,700 recent articles on pediatrics in addition to the 7,854 used in the second edition. The first edition was excellent in its practicality and ease of location of matter, but the author continues to make this material better and easier reading with each revision. As was stated about the other editions, no pediatrician or physician who works with children should be without this book.

**Die Athyreosis und Hypothyreosis im Kindesalter, der endemische Kretinismus.** By Dr. E. Wieland. Price, 19 marks. Pp. 131, with 68 illustrations. Leipzig: Johann Ambrosius Barth, 1940.

This monograph by the celebrated Swiss pediatrician is well worth the perusal of any one who is interested in athyreosis and hypothyreosis in childhood. He

has had a vast amount of experience with this type of condition and especially with endemic cretinism. It is interesting to note that excellent results are being obtained in Switzerland by the use of iodized salt, even in this form of cretinism, which speaks volumes for the value of this preventive measure.

Altogether, this is a worth while monograph.

**The Poison Trail.** By William F. Boos, M.D. Price, $3.00. Pp. 361. New York and Boston: Hale, Cushman and Flint, Publishers, 1939.

This book, written by a Boston toxicologist, is in part autobiographic. While it is written for the layman, it contains much that is interesting to a physician. It describes the author's experience with industrial poisons, compensation work, work with war chemicals and expert testimony in court. The information regarding food poisoning, canning and pasteurization is especially good. The descriptions of cases of accidental poisoning and of poisons used in homicide are interesting to both the physician and the layman.

**Chemical Composition of Foods.** By R. A. McCance and E. M. Widdowson. Price, 4 shillings. Pp. 150, with no illustrations. London: His Majesty's Stationery Office, 1940.

This book contains extensive tables giving the chemical composition of various foods, both raw and cooked, estimated in grams and ounces. It also has tables on the "available" phosphorus and "available" iron in foods. Altogether a useful reference manual, it has, in addition, some recipes for the preparation of common foods.

**Cancer in Childhood.** By Dr. Harold W. Dargeon. Price, $3.00. Pp. 114, with 41 illustrations and 6 charts. St. Louis: C. V. Mosby Company, 1940.

This book is a reprint of several articles on cancer which appeared in the *Journal of Pediatrics* recently. There is a most interesting introductory chapter by Dr. James Ewing, which calls attention to the difference between cancer before puberty and in later life. The book brings to light the fact that malignant disease is much more frequent in childhood than is ordinarily supposed. Each chapter has a good description of the various types of cancer which are found in some portion of the body. Altogether, this is a very worth while book.

**Let's Talk About Your Baby.** Second edition. By H. Kent Tenny, Jr., M.D., with a foreword by Dr. Joseph Brennemann. Price, $1.00. Pp. 115, with 9 illustrations. Minneapolis: University of Minnesota Press, 1940.

This is the second, and a revised, edition. It contains advice to mothers on clothes for the baby, feeding, some usual difficulties that the mother is likely to meet and immunization. A new chapter has been added to record events in the baby's life, such as examinations. The subject matter of the book as a whole is the usual discussion of the baby's care for the guidance of the mother. Any one who liked the first edition will probably like this one.

**Rôle de la constitution dans les maladies infectieuses des enfants.** By Hanna Hirszfeld. Price, paper, $0.70. Pp. 152, with 52 illustrations. Paris: Masson et Cie, 1939.

Dr. Hirszfeld has for many years written interestingly on the role of heredity in disease. Her experience was mostly gained at Josef Pilsudski University in Poland. In this book her ideas are skilfully compressed into a very short space. There are numerous tables and charts to amplify and fortify her conclusions. Although in French, the book is readable and should be perused by any one interested in the subject of heredity.

# Directory of Pediatric Societies*

## INTERNATIONAL

### International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

### International Congress of Pediatrics

American Committee:

Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, 300 Longwood Ave., Boston.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston, Mass. Time: Postponed indefinitely.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

### British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

### Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

### Nederlandsche Vereeniging voor Kindergeneeskunde

President: Prof. Dr. J. van Lookeren Campagne, Hofstraat 16, Gröningen, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

### Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

## NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Julius H. Hess, 104 S. Michigan Ave., Chicago.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Cleveland. Time: June 2-6, 1941.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. J. B. Bilderback, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel Peabody, Memphis, Tenn. Time: Nov. 18-20, 1940.
Region I. Place: New Haven, Conn. Time: March 27-29, 1941.
Region II. Place: Richmond, Va.
Region III. Place: Palmer House, Chicago. Time: May 15-17, 1941.
Region IV. Place: Fairmont Hotel, San Francisco. Time: May 1-3, 1941.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Hot Springs, Va. Time: May 22-24, 1941.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. A. Ashley Weech, 3975 Broadway, New York.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

## SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.
Place: Louisville Ky. Time: Nov. 12-15, 1940.

## STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. Louis M. Earle, 6381 Hollywood, Hollywood, Calif.
Place: Del Monte. Time: May 1941.

### Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

### Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Oliver L. Stringfield, 1416 Bedford St., Stamford.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

### Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.
Place: Chicago. Time: May 1941.

### Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

### Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

### Louisiana State Pediatric Society

President: Dr. H. Aubrey White, Alexandria.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.
Place: Shreveport. Time: April 1941.

### Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

### Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Ralph M. Tyson, 255 S. 17th St., Philadelphia.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Place: Philadelphia, Pa. Time: Sept. 30-Oct. 3, 1940.

### Michigan State Medical Society, Pediatric Section

President: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.
Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.

### Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson
Place: Biloxi. Time: May 12, 1941.

### Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

### New Hampshire Pediatric Society

President: Dr. Colin C. Stewart, Hitchcock Clinic, Hanover.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

### North Carolina Pediatric Society

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

### Oklahoma State Pediatric Society

President: Dr. Ben H. Nicholson, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

### South Carolina Pediatric Society

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

### Tennessee State Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

### Texas Pediatric Society

President: Dr. C. P. Jasperson, 509 Nixon Bldg., Corpus Christi.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Galveston. Time: Oct. 5, 1940.

### Virginia Pediatric Society

President: Dr. S. A. Anderson Jr., 2326 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.

### West Virginia State Medical Society, Section on Pediatrics

President: Dr. Raymond Sloan, 1139–4th Ave., Huntington.
Secretary: Dr. Thomas G. Folsom, 1139–4th Ave., Huntington.

## LOCAL

### Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

### Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

### Bronx Pediatric Society

President: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Secretary: Dr. David Zahn, 2474 Valentine Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

### Brooklyn Academy of Pediatrics

President: Dr. Archibald Smith, Garden City, N. Y.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

### Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and September.

### Chicago Pediatric Society

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. Bengt Hamilton, 826 E. 61st St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

### Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

### Detroit Pediatric Society

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

### Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Stephen C. Redd, 157 Forrest Ave. N. E., Atlanta.
Secretary: Dr. C. Dixon Fowler, Medical Arts Bldg., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

### Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

### Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

### Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

### Milwaukee Pediatric Society

President: Dr. S. F. Morgan, 2577 N. Downer Ave., Milwaukee.
Secretary-Treasurer: Dr. F. R. Janney, 1411 Wauwatosa Ave., Wauwatosa, Wis.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

### New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103 St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

### Northwestern Pediatric Society

President: Dr. Roland E. Nutting, 205 W. 2d St., Duluth, Minn.
Secretary-Treasurer: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

### Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Friday of each alternate month.

### Philadelphia Pediatric Society

President: Dr. Pascal F. Lucchesi, 4000 N. Front St., Philadelphia.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

### Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

### Richmond Pediatric Society

President: Dr. Charles L. Outland, 312 N. 9th St., Richmond, Va.
Secretary-Treasurer: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

### Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

### St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

### Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

### Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Mark Osterlin, Central Michigan Children's Clinic, Traverse City, Mich.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Time: Nov. 15-16, 1940.

### Westchester County Medical Society, Pediatric Section (New York)

President: Dr. M. Bernard Brahdy, 531 E. Lincoln Ave., Mount Vernon.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Ave., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.